



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 11

A. R. Katritzky &
A. J. Boulton

Advances in
Heterocyclic
Chemistry

Volume 11

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Advances in
HETEROCYCLIC
CHEMISTRY

Edited by

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Preface

This, the eleventh volume of *Advances in Heterocyclic Chemistry*, includes surveys of the chemistry of the following groups of heterocyclic compounds: benzo[*b*]thiophenes (B. Iddon and R. M. Scrowston), naphthyridines (W. W. Paudler and T. J. Kress), and quinclidines (L. N. Yakhontov). In addition, R. A. Jones covers the application of physical methods to pyrrole chemistry and a very topical subject, the photochemistry of heterocycles, is reviewed by S. T. Reid.

Suggestions are welcomed for contributions to future volumes; they should be in the form of short synopses.

Thanks are due to the Editorial Board, the publisher, and the authors for their cooperation.

A. R. KATRITZKY
A. J. BOULTON

Norwich, England
November, 1969

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The Photochemistry of Heterocycles

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I. Introduction

The current interest in organic photochemistry¹⁻⁴ is reflected in the increase in the number of publications concerned with the photochemistry of heterocyclic systems. Although it has long been known

¹ J. G. Calvert and J. N. Pitts, "Photochemistry." Wiley, New York, 1966.

² R. O. Kan, "Organic Photochemistry." McGraw-Hill, New York, 1966.

³ A. Schönberg, "Preparative Organic Photochemistry." Springer, Berlin, 1968.

⁴ N. J. Turro, "Molecular Photochemistry." Benjamin, New York, 1965.

that many heterocycles are light-sensitive and that ready photodecomposition does occur, only recently have detailed investigations illustrated the complexity of the rearrangements and other transformations that occur. Furthermore, as later sections of this review will show, considerable use is now being made of photochemically induced reactions in synthesis. The formation of heterocycles, both by photoaddition and photocyclization, is rapidly becoming not only an acceptable, but in some cases, a preferable method of synthesis.

No review of a fast-growing field of this nature can ever hope to be comprehensive, nor, in fact, would the achievement of this be of any lasting value. It is our intention, therefore, to bring to the attention of the reader the more important recent contributions, and in particular to illustrate the generality and scope of many of the processes discussed. The mechanism of each individual photoreaction will not be considered in detail except insofar as it can be seen to impose limitations on the use of the reaction or to affect directly the nature of the photoproduct.

II. Mechanism of Photochemical Reactions

The mechanism of photochemical transformations has been the subject of many articles and monographs and will be discussed only briefly.

Absorption of ultraviolet (UV) or visible light by an organic molecule results in the excitation of an electron to a higher energy level, the energy level difference ΔE being given by the equation $\Delta E = h\nu$. The electron is, in general, promoted to an antibonding orbital, and the process can be accompanied by quantized increases in vibrational and rotational energy levels.

There are two types of electronic transition commonly responsible for photochemically induced reactions in organic molecules. The first of these is the $n \rightarrow \pi^*$ transition in which an electron in a non-bonding atomic orbital is excited to an antibonding π orbital, the excited state being referred to as n, π^* . This occurs in nitrogen-, oxygen-, and sulfur-containing molecules, and the nature of the n, π^* state of the carbonyl function has been the subject of considerable study.^{5, 6} Excitation to the n, π^* state in aldehydes and ketones occurs at approximately 290 nm.

⁵ D. C. Neckers, "Mechanistic Organic Photochemistry." Reinhold, New York, 1967.

⁶ P. J. Wagner and G. S. Hammond, *Advan. Photochem.* **5**, 21 (1968).

The second type of excited state is written as π, π^* and results from a transition in which a π electron is excited to an antibonding π orbital. The light absorbed to produce this transition is generally of shorter wavelength than that for the $n \rightarrow \pi^*$ transition, and the process requires higher energies. The $\pi \rightarrow \pi^*$ transition in ethylene is the result of absorption at 180 nm.

A third transition of less significance is the $n \rightarrow \sigma^*$ transition; this is observed in the photolysis of halogenated compounds.⁷ The σ^* energy level is unusually unstable and the molecule undergoes bond cleavage with the formation of free-radical species. Many photoreactions can, in fact, be thought of in radical terms, and close analogies exist between certain photochemical reactions and free-radical processes.

The excited molecule initially formed from the ground state by absorption of light is in the singlet state; two electrons with antiparallel spins are in orbitals of different energy. Direct excitation to the triplet does not occur. The energy associated with the excited singlet species can be dissipated in one of three ways, by fluorescence (emission of radiation of wavelength similar to that absorbed), by radiationless transitions, and by chemical reaction. Radiationless transitions are of two kinds. The excited species first undergoes internal conversion to the energetically lowest singlet excited state; this is followed either by further internal conversion to a vibrationally excited ground state, or by intersystem crossing to a triplet state involving a change of spin orientation in one electron. The excited triplet state has lower energy than the corresponding singlet state, and also has a significantly longer life (at least 10^{-4} seconds compared with about 10^{-9} seconds for the singlet). Energy is dissipated by the excited triplet in a number of ways; these are phosphorescence (emission of light of longer wavelength than that absorbed), further radiationless transitions including energy transfer to other molecules, and chemical reactions. The exact details of the mechanism of many photochemical reactions are far from clear; in general, most reactions appear to take place in the excited triplet state, although there are authentic examples of reactions occurring in the singlet state and in a vibrationally excited ground state.

In addition to direct excitation, photochemical reactions can be induced by "sensitization." This is the result of energy transfer from an excited molecule and occurs on molecular collision, provided that the energy level to which the acceptor is excited is lower. The use of

⁷ J. R. Majer and J. P. Simons, *Advan. Photochem.* **2**, 137 (1964).

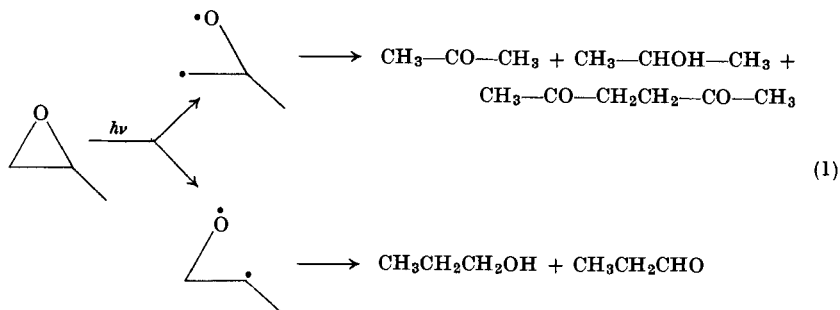
singlet-singlet and, in particular, triplet-triplet energy transfer is of considerable value both in the study of the mechanism of a photo-reaction and in inducing photoreactions in molecules such as alkenes which are difficult to excite directly.

III. Bond Cleavage and Rearrangement

The increase in energy in a molecule on absorption of UV light is sufficient to bring about bond cleavage. As a result, fragmentation and rearrangement of the molecule can occur. The effect on heterocycles is discussed in this section and, for simplicity, the transformations are classified, somewhat arbitrarily, on the basis of ring size; pyrazolines are treated separately. Heterocyclic dienes and heteroaromatic compounds are also discussed separately, and the section is completed by consideration of the photochemistry of heteroaromatic *N*-oxides.

A. THREE-MEMBERED HETEROCYCLES

Early work⁸ on the gas phase photolysis of oxiranes led to the postulation that diradical species resulting from carbon-oxygen bond cleavage were involved in their decomposition. Recent studies⁹ in the liquid phase support the concept of homolytic cleavage of the carbon-oxygen bond, and suggest that this process is followed by a series of radical reactions. In this way, methyloxirane is converted into acetone, isopropanol, propionaldehyde, *n*-propanol, and hexane-2,5-dione; and the formation of these photoproducts has been rationalized in terms of the cleavage of both carbon-oxygen bonds [Eq. (1)]. Similar

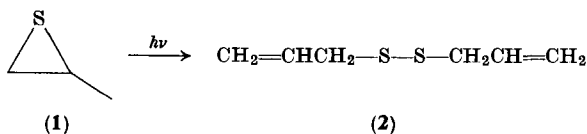


⁸ R. J. Cvetanović and L. C. Doyle, *Can. J. Chem.* **35**, 605 (1957).

⁹ R. J. Gritter and E. C. Sabatino, *J. Org. Chem.* **29**, 1965 (1964).

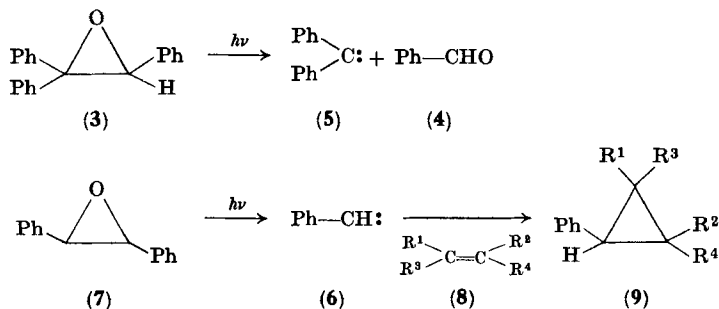
effects are observed in alicyclic epoxides, the principal products of photolysis of cyclohexene oxide being cyclohexanone and cyclohexanol. Oxiranes are also reported¹⁰ to undergo photochemically induced alcoholysis; cyclohexene oxide in this case affording *trans*-2-methoxycyclohexanol in high yield on irradiation in methanol.

Thiiranes appear⁹ to undergo carbon-sulfur bond cleavage more readily, but this process is less well investigated. The only photo-product so far obtained from methylthiirane (1) is the dimeric allyl



disulfide (2). The photosensitized decomposition of aziridine has also been studied.¹¹

Photofragmentation of phenyl-substituted oxiranes has been shown¹² to result in the formation of carbenes; triphenyloxirane (3) on irradiation in methylcyclohexane at 77°K affords benzaldehyde (4) and diphenylmethylene (5), identified by fluorescence and electron paramagnetic resonance (EPR) absorption studies. The most convenient precursor of phenylcarbene (6) is stilbene oxide (7),¹³ and the



stereospecific addition of phenylcarbene to alkenes (8) has been employed as a useful synthesis of phenylcyclopropanes (9).¹³ Phenylcarbene, generated in this way, can also be added in high yield to

¹⁰ K. Tokumaru, *Bull. Chem. Soc. Japan* **40**, 242 (1967).

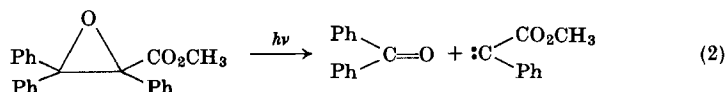
¹¹ R. F. Klemm, *Can. J. Chem.* **45**, 1685 (1967).

¹² A. M. Trozzolo, W. A. Yager, G. W. Griffin, H. Kristinnsson, and I. Sarkar, *J. Am. Chem. Soc.* **89**, 3357 (1967).

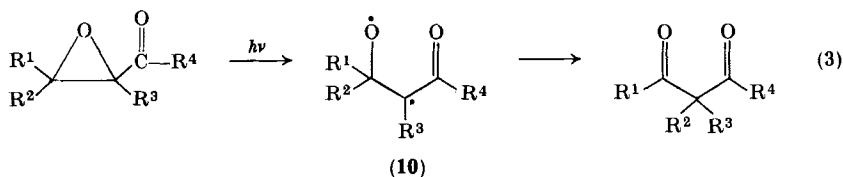
¹³ H. Kristinnsson and G. W. Griffin, *J. Am. Chem. Soc.* **88**, 1579 (1966).

but-2-yne to give the phenyl-substituted cyclopropene,¹³ and undergoes insertion reactions with *n*-pentane to form the three possible phenyl-substituted alkanes.¹⁴

Formation of these carbenes may well involve a two-step homolytic cleavage, but the extension of this process to the formation of phenylcyanocarbene and phenylmethoxycarbonylcarbene from the appropriately substituted oxirane led to the suggestion that heterolytic cleavage of the carbon-carbon bond might be the initial step.¹⁵ This would account for the formation of phenylmethoxycarbonylcarbene in preference to diphenylmethylene in the photolysis of 2-methoxycarbonyl-2,3,3-triphenyloxirane [Eq. (2)].



Recently, considerable interest has been shown in the photochemistry of α,β -epoxyketones.¹⁶ Although the photochemistry of this system is undoubtedly the result of an $n \rightarrow \pi^*$ excitation in the carbonyl function, the orbital overlap with the "bent bonds" of the three-membered ring, for which there is considerable evidence,¹⁶ is also implicated in the process. The major product of irradiation of an α,β -epoxyketone is the corresponding β -diketone, the result of oxirane ring cleavage and migration of a β -substituent to the α -position [Eq. (3)]. Other photoproducts arise mainly from the β -diketone.



The unusual order of migratory aptitude, benzhydryl and benzyl > hydrogen > methylene > methyl \gg phenyl, is accounted for in terms of the intermediate (10) formed directly from the excited singlet state.¹⁷

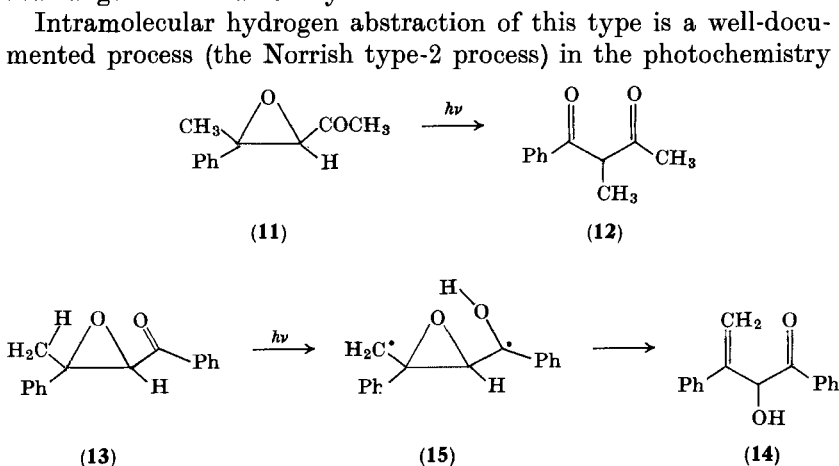
¹⁴ H. Dietrich, G. W. Griffin, and R. C. Petterson, *Tetrahedron Letters* 153 (1968).

¹⁵ P. C. Petrellis and G. W. Griffin, *Chem. Commun.* 691 (1967).

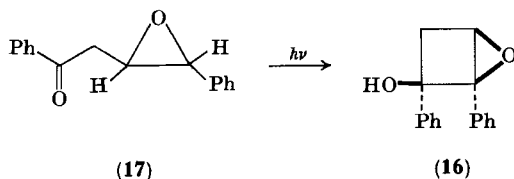
¹⁶ A. Padwa, in "Organic Photochemistry" (O. L. Chapman, ed.), Vol. 1, p. 91. Dekker, New York, 1967.

¹⁷ C. S. Markos and W. Reusch, *J. Am. Chem. Soc.* **89**, 3363 (1967).

Other factors including the environment of the carbonyl group also appear to influence the course of this rearrangement. While 3,4-epoxy-4-phenylpentan-2-one (**11**) is rearranged to the diketone (**12**) in the usual manner, *trans*-1-benzoyl-1,2-epoxy-2-phenylpropane (**13**) undergoes a different rearrangement to give 1,3-diphenyl-2-hydroxybut-3-en-1-one (**14**),¹⁸ presumably via an initial intramolecular hydrogen abstraction from the γ -carbon atom (**15**), followed by ring cleavage. The corresponding *cis* isomer, in which hydrogen abstraction by the benzoyl group from the methyl group is no longer possible, is not rearranged in the same way.



of ketones, and additionally leads to the formation of cyclobutanols. The cyclobutanol (**16**) was, in fact, obtained as one of the products of photolysis of the β,γ -epoxyketone (**17**).¹⁹

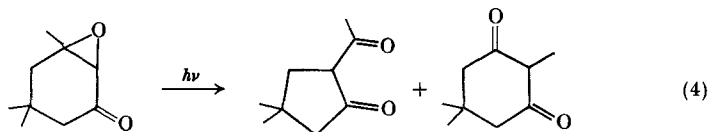


The study of the photochemical rearrangements of α,β -epoxyketones has been extended to include cyclic systems and, in particular,

¹⁸ H. E. Zimmerman, B. R. Cowley, C. Y. Tseng, and J. W. Wilson, *J. Am. Chem. Soc.* **86**, 947 (1964).

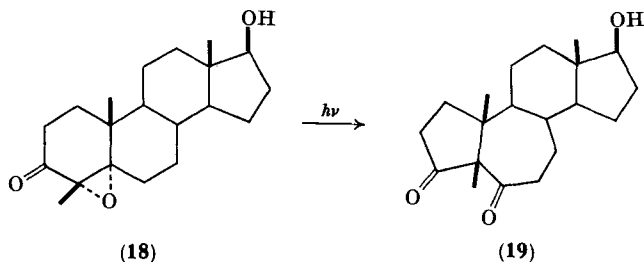
¹⁹ A. Padwa, D. Crumrine, R. Hartman, and R. Layton, *J. Am. Chem. Soc.* **89**, 4435 (1967).

steroidal molecules in which a detailed study of the stereochemistry can easily be made. Isophorone oxide, for example, is converted into the two possible β -diketones [Eq. (4)].²⁰

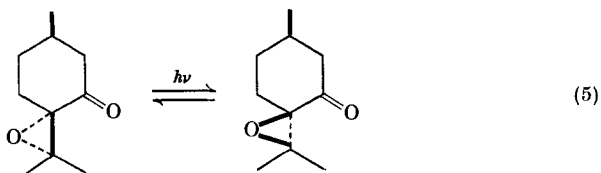


A stereospecific rearrangement is observed in the photolysis of 17 β -hydroxy-4 α ,5 α -epoxy-4 β -methylandrostan-3-one (**18**) to give the β -diketone (**19**)²¹; the analogous 4 β ,5 β -epoxysteroid is converted in the same manner into the diketone with a 5 α -methyl group.

There are, however, a number of exceptions to this specificity; and in some systems, photoisomerization is known to occur. One such



example is the reversible isomerization of α - and β -pulegone oxides [Eq. (5)].²⁰

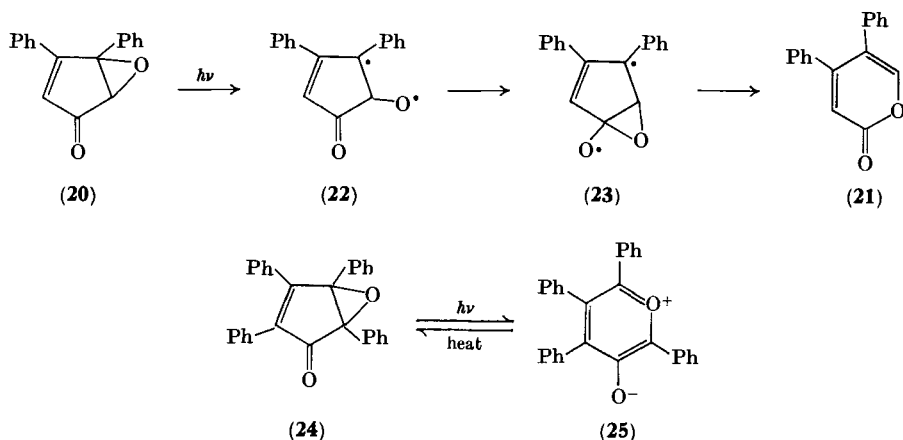


The photorearrangement of certain epoxycyclopentenones takes a different course to yield 2-pyrone derivatives; one example is the conversion of 3,4-diphenyl-4,5-epoxycyclopent-2-en-1-one (**20**) into 4,5-diphenyl-2-pyrone (**21**), and this can be rationalized by assuming cleavage of the oxirane to give the diradical (**22**) or its equivalent,

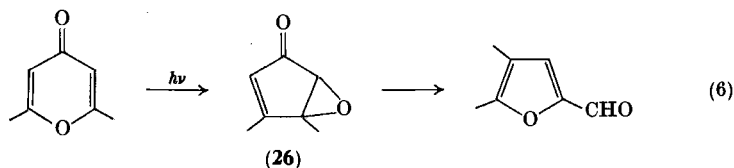
²⁰ C. K. Johnston, B. Dominy, and W. Reusch, *J. Am. Chem. Soc.* **85**, 3894 (1963).

²¹ H. Wehrli, C. Lehmann, K. Schaffner, and O. Jeger, *Helv. Chim. Acta* **47**, 1336 (1964).

followed by rearrangement to the intermediate (23).²² Other epoxy-cyclopentenones also undergo this photoreaction, and in the case of the tetraphenyl derivative (24), an additional product is the pyrylium 3-oxide (25)²³; this is not, however, an intermediate in the formation of the corresponding pyrone. Both processes are observed in the photolysis of substituted 2,3-epoxyindanones.²⁴



An epoxycyclopentenone (26) is also thought to be an intermediate in the photochemical conversion of 2,6-dimethylpyrone into 4,5-dimethylfurfuraldehyde²⁵ [Eq. (6)], but the reasons for the formation of the furan rather than a 2-pyrone are not clear.



The photoreaction characteristic of epoxyketones is not observed in the corresponding aziridine or thiirane derivatives. In the compounds so far examined, the result of photolysis is usually photoextrusion of the heteroatom. In this way, *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine is converted in aqueous ethanol into a

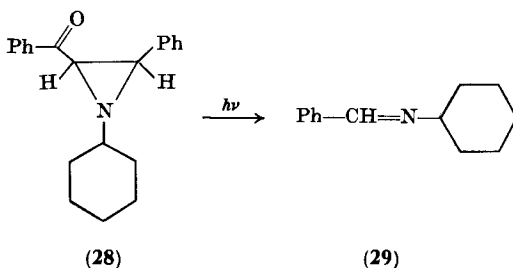
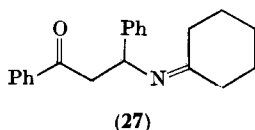
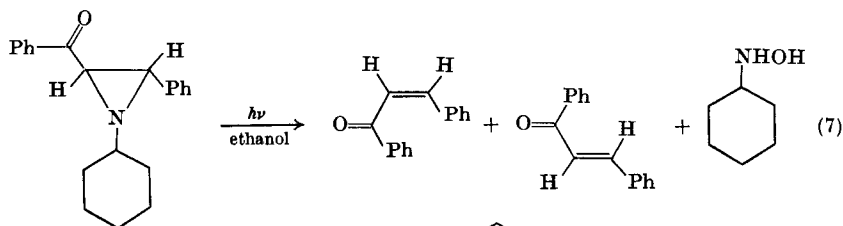
²² A. Padwa, *Tetrahedron Letters* 813 (1964).

²³ J. M. Dunstan and P. Yates, *Tetrahedron Letters* 505 (1964).

²⁴ H. E. Zimmerman and R. D. Simkin, *Tetrahedron Letters* 1847 (1964).

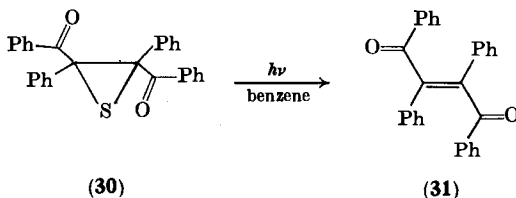
²⁵ P. Yates and I. W. J. Smith, *J. Am. Chem. Soc.* **85**, 1208 (1963).

mixture of *cis*- and *trans*-benzalacetophenone and *N*-cyclohexyl-hydroxylamine [Eq. (7)].²⁶ When the photolysis is carried out in pentane solution, cyclohexanone and the imine (27) are obtained in



addition to *cis*- and *trans*-benzalacetophenone. The mechanism of this transformation has been discussed in detail.²⁶ One important feature is the relative position of the phenyl and the benzoyl groups, and irradiation of the *cis* isomer (28), also in aqueous ethanol, affords the Schiff's base (29) as the major product along with acetophenone.

The investigation of oxothiiranes appears to have been limited to the study of *trans*-1,2-dibenzoyl-1,2-diphenylthiirane (30) which is initially converted into *trans*-dibenzoylstilbene (31).²⁷ The photolysis



²⁶ A. Padwa and L. Hamilton, *J. Am. Chem. Soc.* **89**, 102 (1967).

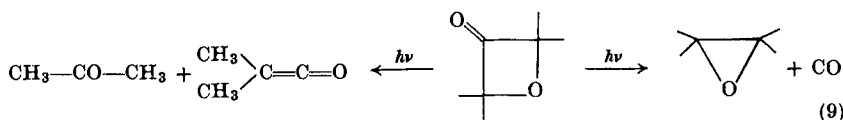
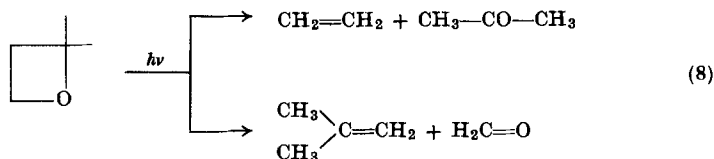
²⁷ A. Padwa and D. Crumrine, *Chem. Commun.* 506 (1965).

of the corresponding sulfoxide is of considerable interest, as it leads to the isolation, for the first time, of a monothiobenzil.²⁸

B. FOUR-MEMBERED HETEROCYCLES

Reports of the photolysis of four-membered heterocycles are scattered throughout the literature, but no systematic investigation has been carried out. The principal process is again one of ring cleavage, and thietane is fragmented²⁹ in this way in high yield to ethylene. The analogous five- and six-membered sulfur heterocycles also undergo photochemically induced ring cleavage.²⁹

The cleavage reaction occurring in oxetanes has been examined in more detail. 2,2-Dimethyloxetane, for example, decomposes by two alternate pathways [Eq. (8)] to give a mixture of ethylene and acetone, and 2-methylpropene and formaldehyde.³⁰ A similar fragmentation occurs³¹ in tetramethyloxetan-3-one [Eq. (9)] on irradiation in polar



solvents to give acetone and dimethylketene. In nonpolar solvents, decarbonylation also occurs and yields tetramethyloxirane [Eq. (9)]. Such decarbonylations are characteristic of cyclic ketones and are common, particularly in the vapor phase.³²

²⁸ D. C. Dittmer, G. C. Levy, and G. E. Kuhlmann, *J. Am. Chem. Soc.* **89**, 2793 (1967).

²⁹ W. Haines, R. V. Helm, G. Cook, and J. Ball, *J. Am. Chem. Soc.* **78**, 5213 (1956).

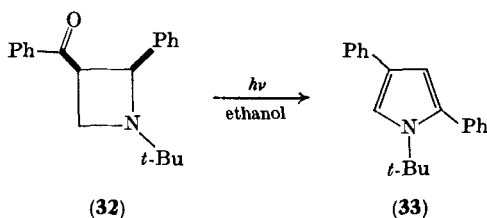
³⁰ J. D. Magerum, J. N. Pitts, J. G. Rutgers, and S. Searles, *J. Am. Chem. Soc.* **81**, 1549 (1959).

³¹ P. J. Wagner, C. A. Stout, S. Searles, and G. S. Hammond, *J. Am. Chem. Soc.* **88**, 1242 (1966).

³² R. Srinivasan, *Advan. Photochem.* **1**, 83 (1963).

Ring cleavage is also reported³³ for perfluoro-1,2-oxazetidines, and photochemical cleavage of the β -lactam system is probably responsible for the photodegradation of both cephalosporin³⁴ and the penicillins.³⁵

A reaction of particular interest is the photoinduced ring expansion in 95% yield of *cis*-1-*t*-butyl-2-phenyl-3-benzoylazetidine (**32**) to 1-*t*-butyl-2,4-diphenylpyrrole (**33**).³⁶ This is regarded as the first example of the migration of an alkyl group from the α -position to the excited carbonyl group ($n \rightarrow \pi^*$).

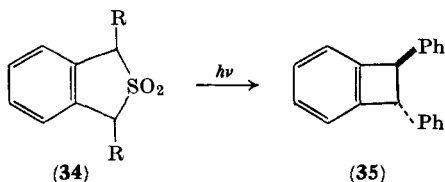


C. FIVE- AND SIX-MEMBERED HETEROCYCLES

A large number of apparently unrelated ring cleavage and rearrangement reactions are known to occur in five- and six-membered nonaromatic heterocycles. These are best considered in terms of the nature of the heterocyclic system.

1. Sulfur Heterocycles

The photolysis of cyclic sulfones leads to carbon-sulfur bond cleavage and the extrusion of sulfur dioxide. In the diphenyl derivative (**34**; R = Ph), this is accompanied by the formation of a new carbon-carbon bond, and the product is *trans*-1,2-diphenylbenzocyclobutene



³³ R. E. Banks, R. N. Haszeldine, and H. Sutcliffe, *J. Chem. Soc.* 4066 (1964).

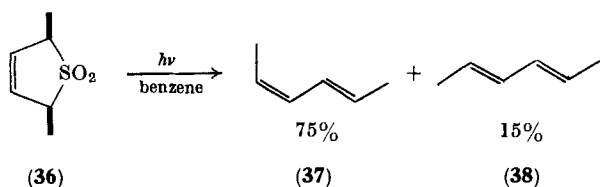
³⁴ A. L. Demain, *Nature* **210**, 5034 (1966).

³⁵ W. O. Godtfredson, W. von Daehne, and S. Vangedal, *Experientia* **23**, 280 (1967).

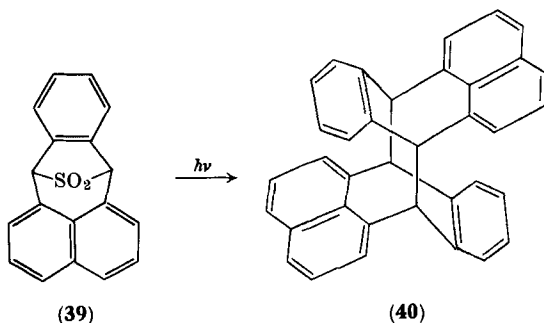
³⁶ A. Padwa, R. Gruber, and L. Hamilton, *J. Am. Chem. Soc.* **89**, 3077 (1967).

(35).³⁷ The corresponding naphthalene sulfone behaves similarly.³⁷ No reaction is observed in the unsubstituted analog (**34**; R=H) even in the presence of a sensitizer, and the extrusion of sulfur dioxide is therefore believed to occur in a vibrationally excited ground state.

A different pathway appears to operate in the benzene-photo-sensitized decomposition of the sulfolene (**36**)³⁸; formation of the diene (**37**) as the major product is in accord with the prediction of concerted conrotatory fragmentation in the excited state. Fragmentation in a vibrationally excited state would yield the alternative diene (**38**) as the major product. Similar observations³⁸ in related sulfolenes support this conclusion.



Irradiation of the sulfone (39) in benzene gave, not the strained cyclobutene derivative, but the pleiadene dimer (40).³⁹



The first reported⁴⁰ photorearrangement of a sulfoxide occurs in 2,2-dimethylthiachroman 1-oxide; on irradiation in benzene, this is converted into 2-isopropylbenzo[*b*]thiophene. The detailed mechanism of this transformation is uncertain, but it has been rationalized by assuming that intramolecular hydrogen abstraction by the excited

³⁷ M. P. Cava, R. H. Schlessinger, and J. P. Van Meter, *J. Am. Chem. Soc.* **86**, 3173 (1964).

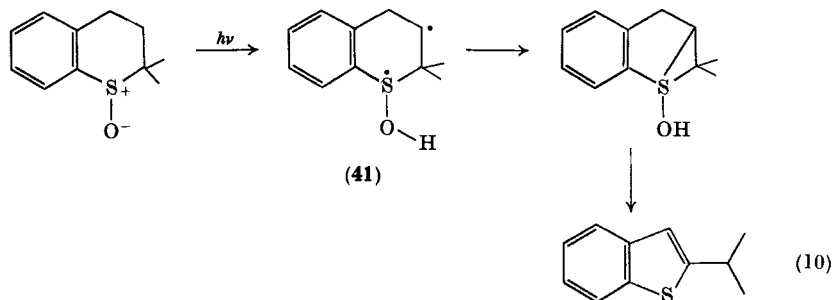
³⁸ J. Saltiel and L. Metts, *J. Am. Chem. Soc.* **89**, 2232 (1967).

³⁹ M. P. Cava and R. H. Schlessinger, *Tetrahedron* **21**, 3073 (1965).

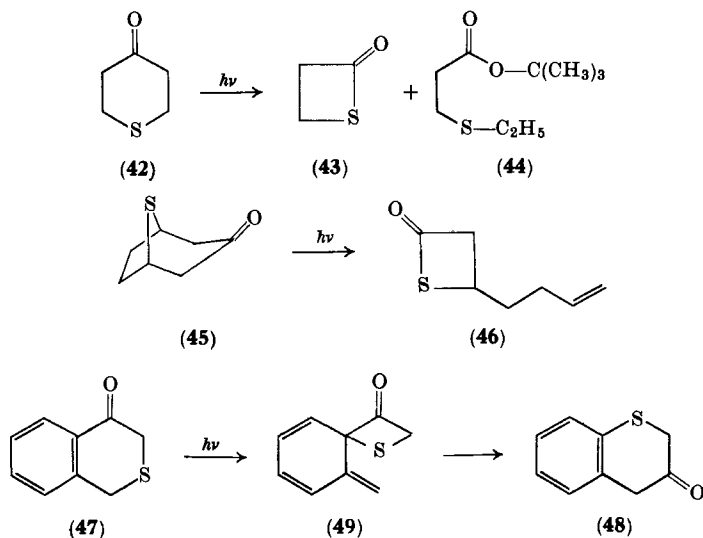
⁴⁰ R. A. Archer and B. S. Kitchell, *J. Am. Chem. Soc.* **88**, 3462 (1966).

sulfoxide group occurs to give a species represented by **41**. Bond formation, followed by dehydration and rearrangement, yields the benzo[*b*]thiophene [Eq. (10)].

Preliminary accounts of the photochemistry of β - and γ -oxosulfides have appeared in the literature. Thiacyclohexan-4-one (**42**), on irradiation in *t*-butanol, is converted into β -thiolactone (**43**) and the



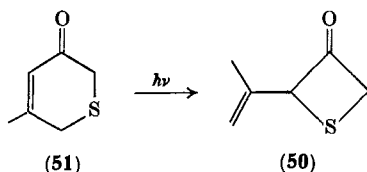
t-butyl ester (**44**)⁴¹; presumably, ethylene must also be formed. 8-Thiabicyclo[3.2.1]octan-3-one (**45**) undergoes an analogous ring contraction to give the substituted β -thiolactone (**46**) as the principal photoproduct.⁴¹ Photolysis in cyclohexane of isothiachroman-4-one (**47**), and many of its derivatives, yields thiachroman-3-one (**48**).⁴²



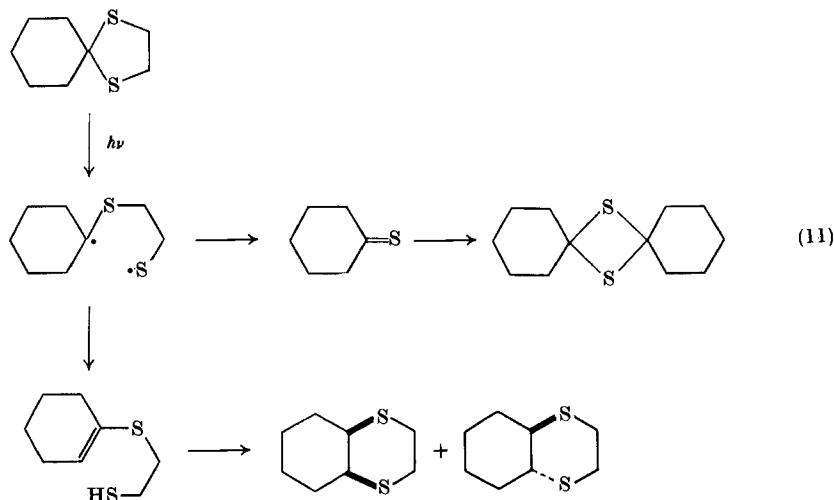
⁴¹ P. Y. Johnson and G. A. Berchtold, *J. Am. Chem. Soc.* **89**, 2761 (1967).

⁴² W. C. Lumma and G. A. Berchtold, *J. Am. Chem. Soc.* **89**, 2761 (1967).

There is convincing evidence for the intermediacy of the triene (49) in this transformation; in particular, the stable thiacyclobutanone (50) is obtained in 30% yield on photolysis of 51.



The photochemistry of certain cyclic mercaptols has been investigated,⁴³ and the two major pathways can be interpreted in terms of initial carbon-sulfur bond cleavage [Eq. (11)].



2. Oxygen Heterocycles

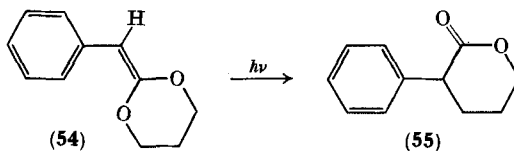
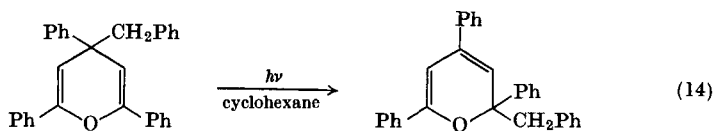
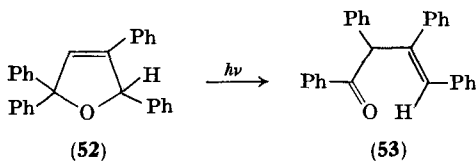
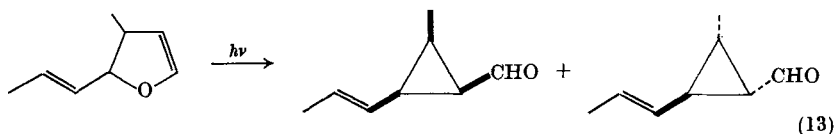
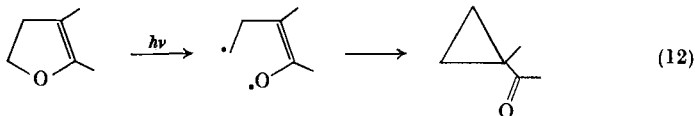
2,3-Dimethyl-4,5-dihydrofuran undergoes photochemical rearrangement in diethyl ether to form 1-acetyl-1-methylcyclopropane together with smaller quantities of *cis*- and *trans*-3-methylbut-3-en-2-one and 3-methylbut-4-en-2-one.⁴⁴ The formation of these products must arise by carbon-oxygen bond cleavage [Eq. (12)]. Analogous ring contractions have been recorded in 2-methyl-4,5-dihydrofuran,⁴⁴

⁴³ J. D. Willett, J. R. Grunwell, and G. A. Berchtold, *J. Org. Chem.* **33**, 2297 (1968).

⁴⁴ D. E. McGreer, M. G. Vinje, and R. S. McDaniel, *Can. J. Chem.* **43**, 1417 (1965).

in alkylated 2-vinyl-2,3-dihydrofuran derivatives⁴⁵ [see, for example, Eq. (13)], and in phenyl-substituted dihydrofurans.^{46, 47} A similar ring contraction is thought to be implicated in the photoisomerization of five-membered aromatic heterocycles. 2,3,5,5-Tetraphenyl-2,5-dihydrofuran (**52**), however, behaves differently; on irradiation in benzene, carbon-oxygen bond cleavage occurs,⁴⁷ and is followed by C-5 to C-4 phenyl migration to give 1,2,3,4-tetraphenylbut-3-en-1-one (**53**).

Two other rearrangements worthy of mention are the conversion of 4-benzyl-2,4,6-triphenyl-4*H*-pyran into 2-benzyl-2,4,6-triphenyl-2*H*-pyran [Eq. (14)],⁴⁸ and photolysis of the phenylketene acetal (**54**) in cyclohexane which yields the lactone (**55**).⁴⁹



⁴⁵ J. Wiemann, N. Thoai, and F. Weisbuch, *Bull. Soc. Chim. France* 575 (1966).

⁴⁶ P. Scribe, M. R. Monot, and J. Wiemann, *Tetrahedron Letters* 5157 (1967).

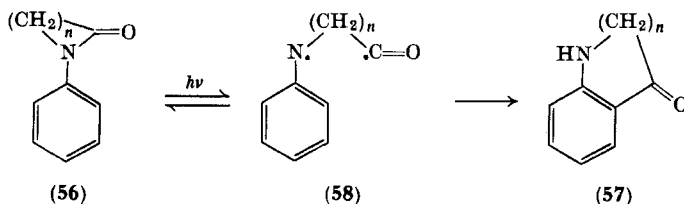
⁴⁷ D. W. Boykin and R. E. Lutz, *J. Am. Chem. Soc.* **86**, 5046 (1964).

⁴⁸ K. Dimroth, K. Wolf, and H. Kroke, *Ann. Chem.* **678**, 183 (1964).

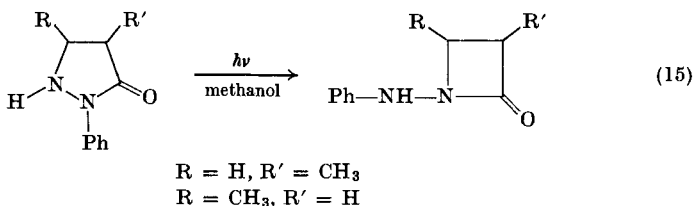
⁴⁹ J. E. Baldwin and L. E. Walker, *J. Am. Chem. Soc.* **88**, 3769 (1966).

3. Nitrogen Heterocycles

Ring cleavage reactions are by far the most common transformations observed on photolysis of nonaromatic nitrogen heterocycles. Cleavage of the carbon–nitrogen bond in lactams appears to be an especially facile process. Thus, irradiation of a series of *N*-phenyl lactams (**56**) yields a nitrogen heterocycle of general structure **57**, presumably via the diradical species (**58**).⁵⁰ The related photorearrangement of anilides to *o*- and *p*-acylanilines is well known. The novel ring contraction⁵¹ of certain 1-phenyl-5-pyrazolidones to substituted β -lactams [Eq. (15)] can also be rationalized in terms of such bond cleavage. Both the 3-methyl and 4-methyl derivatives



undergo this transformation, which provides the first undisputed synthesis of a 1-aminoazetidin-2-one.⁵¹



Photochemical cleavage of 4,6,6-trimethyl-5,6-dihydro-1*H*-pyrid-2-one (**59**) in *t*-butanol or aqueous solution surprisingly yields non-conjugated (**60**) and conjugated (**61**) amides; acetone is also isolated.⁵² The *N*-acetyl derivative of (**59**) is unreactive under identical conditions. Various mechanisms have been proposed⁵² to account for this photoreaction, which is undoubtedly the result of excitation of the α,β -unsaturated carbonyl function. Ring cleavage is also reported to occur in maleic hydrazide⁵³ and in dihydrothymidine.⁵⁴

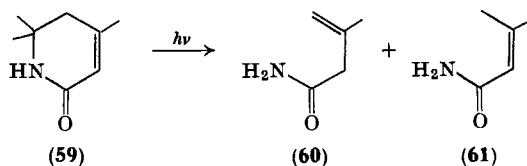
⁵⁰ M. Fischer, *Tetrahedron Letters* 4295 (1968).

⁵¹ S. N. Ege, *Chem. Commun.* 759 (1968).

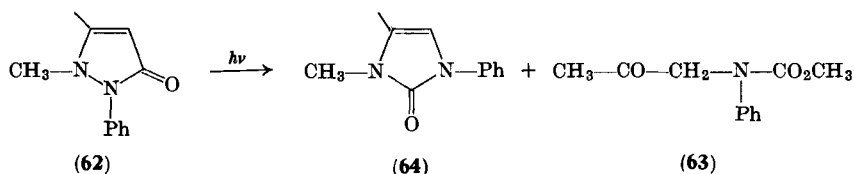
⁵² E. Cavalieri and D. Gravel, *Tetrahedron Letters* 3973 (1967).

⁵³ A. Stoessl, *Can. J. Chem.* **43**, 2430 (1965).

⁵⁴ Y. Kondo and B. Witkop, *J. Am. Chem. Soc.* **90**, 3258 (1968).



Preliminary reports on the photochemistry of 3-pyrazolin-5-one derivatives have been made. 2,3-Dimethyl-1-phenyl-3-pyrazolin-5-one (antipyrene; **62**) undergoes ring cleavage on irradiation in methanol to give the carbamate (**63**), methyl phenylcarbamate, *N*-methyl-*N'*-phenyloxamide, and oxanilide.⁵⁵ In addition, a 10% yield of the imidazolinone (**64**) is obtained by a rearrangement which is at least formally related to that encountered in the aromatic heterocycles. The corresponding 4-dimethylaminopyrazolinone (amidopyrene) also undergoes ring cleavage and rearrangement, and these transformations appear to be solvent-dependent.^{56, 57}



The photochemistry of certain *N*-substituted heterocycles has also been studied. As part of a continuing investigation of the photolysis of *N*-nitroso compounds in solution, the conversion of *N*-nitroso-3-azabicyclo[3.2.2]nonane (**65**) into the oxime (**66**) by photolysis in the presence of acid was reported.⁵⁸ *N*-Nitrosopyrrolidine is similarly transformed. The mechanism of this reaction is said⁵⁸ to involve elimination of NOH with the formation of an imine as intermediate, and, in fact, in the photolysis of 2-ethyl-*N*-nitrosopiperidine (**67**), the tetrahydropyridine (**68**) is the major product. This mechanism certainly does not operate in the photolysis of *N*-nitroso-2-azacyclo-octanone, which can be rationalized on the basis of an intramolecular hydrogen transfer [Eq. (16)].⁵⁹ Acyclic *N*-nitrosoamides behave in a similar fashion to *N*-nitrosoamines.⁶⁰

⁵⁵ S. N. Ege, *Chem. Commun.* 488 (1967).

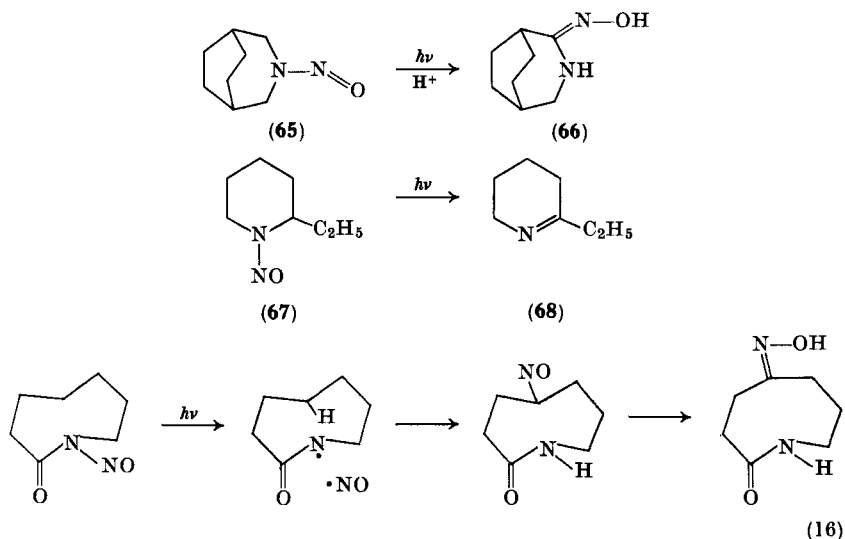
⁵⁶ J. Reisch and A. Fitzek, *Tetrahedron Letters* 4513 (1967).

⁵⁷ J. Reisch and R. Pagnucco, *Chem. Ind. (London)* 1646 (1967).

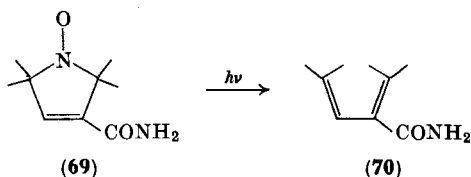
⁵⁸ Y. L. Chow, *Can. J. Chem.* **45**, 53 (1967).

⁵⁹ O. E. Edwards and P. S. Rosich, *Can. J. Chem.* **45**, 1287 (1967).

⁶⁰ Y. L. Chow and A. C. H. Lee, *Can. J. Chem.* **45**, 311 (1967).



Elimination of nitric oxide from 3-carbamoyl-2,2,5,5-tetramethylpyrroline 1-oxyl (**69**) was observed on photolysis in benzene, and an almost quantitative yield of the diene (**70**) was obtained.⁶¹ Ring-saturated nitroxides appear to be unaffected by irradiation of the same wavelength.

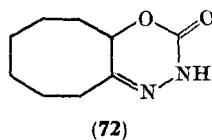
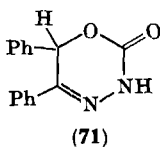


4. Oxygen-Nitrogen Heterocycles

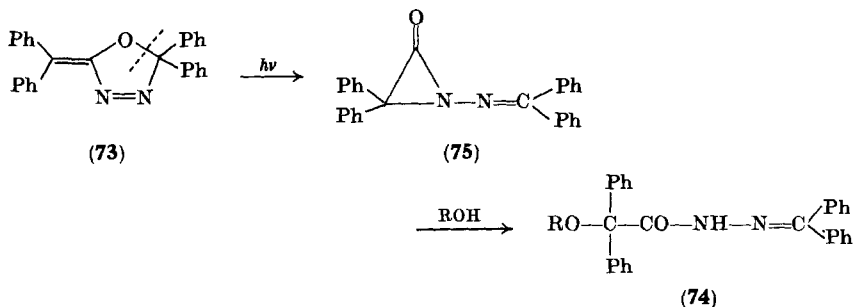
Photoinduced ring cleavage also occurs readily in heterocyclic systems containing both oxygen and nitrogen. A series of dihydro-oxadiazinones, for example, undergo decomposition, and the results obtained parallel those observed on thermal decomposition; *cis*- and *trans*-stilbene are obtained from the diphenyl derivative (**71**), whereas *cis*-cyclooctene is the major product of photolysis of the fused cyclooctane (**72**).⁶²

⁶¹ J. F. W. Keana and F. Baitis, *Tetrahedron Letters* 365 (1968).

⁶² B. Fuchs and M. Rosenblum, *J. Am. Chem. Soc.* **90**, 1061 (1968).

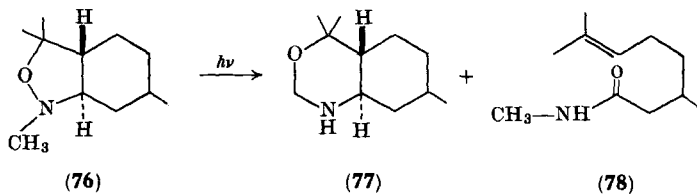


The photochemical decomposition of 2,2-diphenyl-5-(diphenylmethylene)-1,3,4-oxadiazoline (**73**) is solvent-dependent.⁶³ In benzene,



diphenylketene and diphenyldiazomethane are reversibly formed, whereas in an alcohol, solvent incorporation occurs and the product has the structure **74**. A common intermediate (**75**), formed by initial carbon-oxygen bond cleavage, is proposed.⁶³

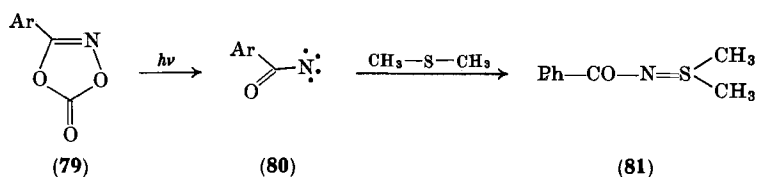
The *N*-methylisoxazolidine (**76**) undergoes ring expansion to the tetrahydro-1,3-oxazine (**77**) on photolysis in hexane⁶⁴; the rearrangement can be accounted for in terms of an initial nitrogen-oxygen bond cleavage, followed by hydrogen transfer from the methyl group to the nitrogen atom and subsequent carbon-oxygen bond formation. A small quantity of the unsaturated amide (**78**) is obtained by the alternative carbon-oxygen bond cleavage.



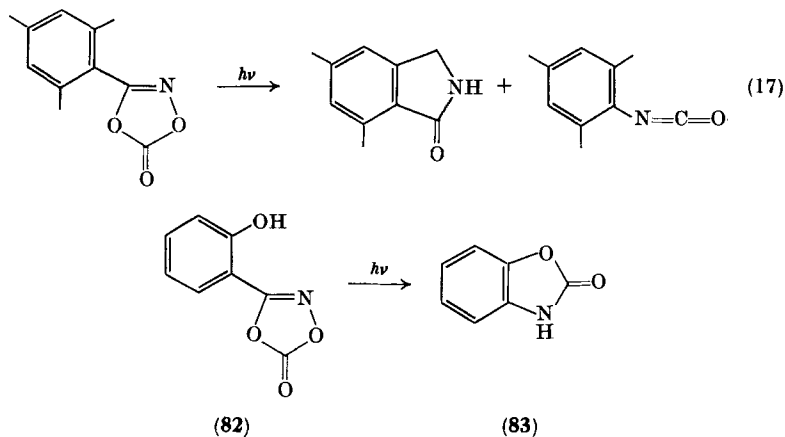
⁶³ C. J. Michejda, *Tetrahedron Letters* 2281 (1968).

⁶⁴ N. A. Le Bel, T. A. Lajiness, and D. B. Ledlie, *J. Am. Chem. Soc.* **89**, 3076 (1967).

The photochemistry of 3-aryl-substituted 1,4,2-dioxazol-2-in-5-ones (**79**) can be interpreted in terms of ring cleavage and loss of carbon dioxide with the formation of an acyl nitrene (**80**); such nitrenes are also formed by the photolysis of acid azides. In dimethyl sulfide, therefore, the 3-phenyl derivative itself (**79**; Ar = Ph) is converted into the photoproduct (**81**).⁶⁵ When the phenyl group is substituted in



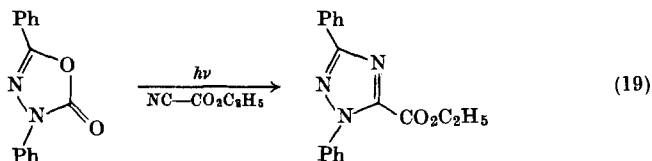
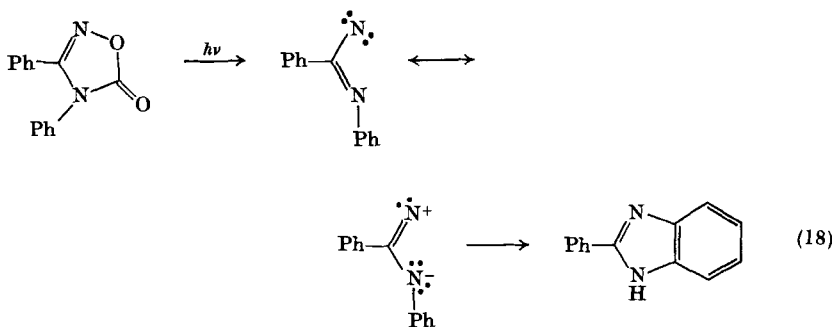
the *ortho* position, cyclization of the intermediate nitrene may occur⁶⁵ [see, for example, Eq. (17)]. The conversion⁶⁵ of the *o*-hydroxy derivative (**82**) into benzoxazolone (**83**) probably involves rearrangement to the isocyanate prior to cyclization.



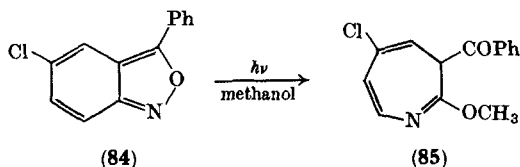
3,4-Diphenyl-1,2,4-oxadiazolin-5-one undergoes a similar cleavage with evolution of carbon dioxide on photolysis in dioxane [Eq. (18)].⁶⁶ The reactive intermediate formed on photolysis of 2,4-diphenyl-1,3,4-oxadiazolin-5-one forms dihydropyrazole, pyrazole, and 1,2,4-triazole derivatives by cycloaddition to conjugated alkenes, acetylenes, and nitriles [Eq. (19)], respectively.⁶⁶

⁶⁵ J. Sauer and K. K. Mayer, *Tetrahedron Letters* 319 (1968).

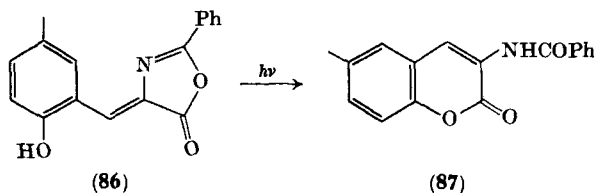
⁶⁶ J. Sauer and K. K. Mayer, *Tetrahedron Letters* 325 (1968).



Photochemically induced nitrogen-oxygen bond cleavage is also thought to be the initial step in the conversion of 6-chloro-3-phenylanthranil (**84**) into 3-benzoyl-5-chloro-2-methoxy-3*H*-azepine (**85**) in methanol.⁶⁷ Analogous transformations are reported in 3-methyl- and 6-chloroanthranil.⁶⁷



Finally, 2-phenyl-4-(2-hydroxy-5-methylbenzylidene)-5-oxazolone (**86**) is converted by irradiation into 3-benzamido-6-methylcoumarin (**87**).⁶⁸ The reasons for this rearrangement, however, are not clear.

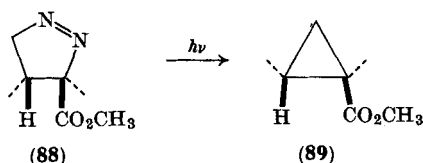


⁶⁷ M. Ogata, H. Kano, and H. Matsumoto, *Chem. Commun.* 397 (1968).

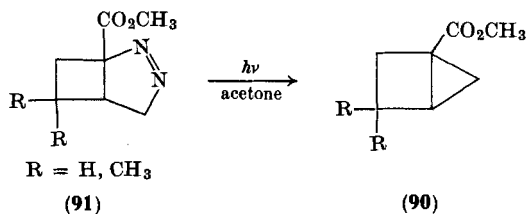
⁶⁸ R. Walter, T. C. Purcell, and H. Zimmer, *J. Heterocyclic Chem.* 3, 235 (1966).

D. 1-PYRAZOLINES

1-Pyrazolines, in general, undergo a photochemically induced ring contraction in solution to form a cyclopropane derivative and nitrogen. This process, unlike some equivalent thermal decompositions, is stereospecific, and methyl-*cis*-3,4-dimethyl-1-pyrazoline-3-carboxylate (**88**) is converted in high yield into methyl-*cis*-1,2-dimethylcyclopropane carboxylate (**89**).⁶⁹ This route is of considerable preparative



value, particularly since such pyrazolines are readily obtainable by the cycloaddition of diazomethane to alkenes. Fused cyclopropane systems are relatively easily synthesized by this method, an illustration being the formation of the substituted bicyclo[2.1.0]pentane (**90**) from the pyrazoline (**91**).^{70, 71}



Other analogous photodecompositions of 1-pyrazolines are known,^{72, 73} while the photolysis⁷⁴ of 3,3*a*,5*a*,6,6*a*,6*b*-hexahydro-3,6-ethenocycloprop[*g*]indazole gives rise to products resulting from bond cleavage and further rearrangement [Eq. (20)].

The photolysis of 2,3-diazabicyclo[2.2.1]hept-2-ene (**92**) has been examined in some detail in the gas phase.⁷⁵ The expected primary

⁶⁹ T. V. Van Auken and K. L. Rinehart, *J. Am. Chem. Soc.* **84**, 3736 (1962).

⁷⁰ T. H. Kinstle, R. L. Welch, and R. W. Exley, *J. Am. Chem. Soc.* **89**, 3660 (1967).

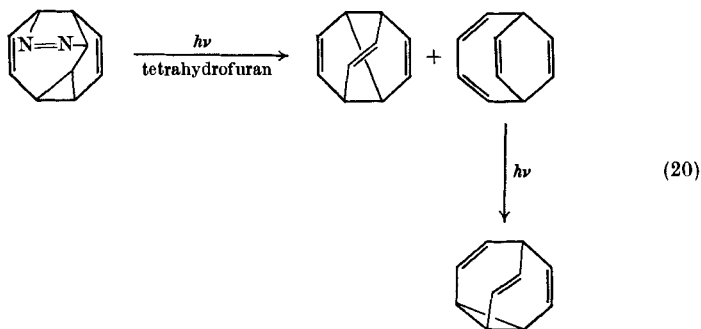
⁷¹ P. G. Gassman and K. T. Mansfield, *J. Org. Chem.* **32**, 915 (1967).

⁷² K. Kocsis, P. G. Ferrini, D. Arigoni, and O. Jeger, *Helv. Chim. Acta* **43**, 2178 (1960).

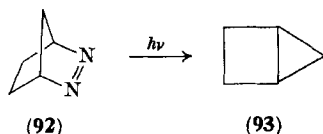
⁷³ M. Franck-Neumann, *Tetrahedron Letters* 2979 (1968).

⁷⁴ S. Masamune, H. Zenda, M. Wiesel, N. Nakatsuka, and G. Bigam, *J. Am. Chem. Soc.* **90**, 2727 (1968).

⁷⁵ T. F. Thomas, C. I. Sutin, and C. Steel, *J. Am. Chem. Soc.* **89**, 5107 (1967).



product, bicyclo[2.1.0]pentane (**93**), has sufficient vibrational excitation energy to undergo a series of unimolecular reactions, yielding cyclopentene, cyclopentadiene, and penta-1,4-diene in addition to the bicyclic hydrocarbon.



The photolysis of the 4-alkylidene-1-pyrazoline (**94**) gives rise to two isomeric methylene cyclopropanes (**95** and **96**).⁷⁶ The available evidence points to the intermediacy of a trimethylenemethyl species (**97**) in the triplet state which can cyclize in three ways. The same species is postulated in the photolysis of a series of 4-alkylidene-1-pyrazoline-3-carboxylates.⁷⁷ This appears to be a general route to derivatives of trimethylenemethyl; trimethylenemethyl itself has been generated from 4-methylene-1-pyrazoline and the triplet nature of the intermediate identified by electron spin resonance (ESR) spectroscopy.⁷⁸

3,7-Diphenyl-1,2-diaza-1-cycloheptene (**98**) undergoes a similar type of ring contraction, accompanied by the formation of nitrogen, on exposure to UV light.⁷⁹ In the solid state, this photolysis is stereospecific and the product is *cis*-1,2-diphenylcyclopentane (**99**). Both thermal and photolytic decompositions in solution yield a mixture of *cis*- and *trans*-1,2-diphenylcyclopentane in addition to *cis*- and

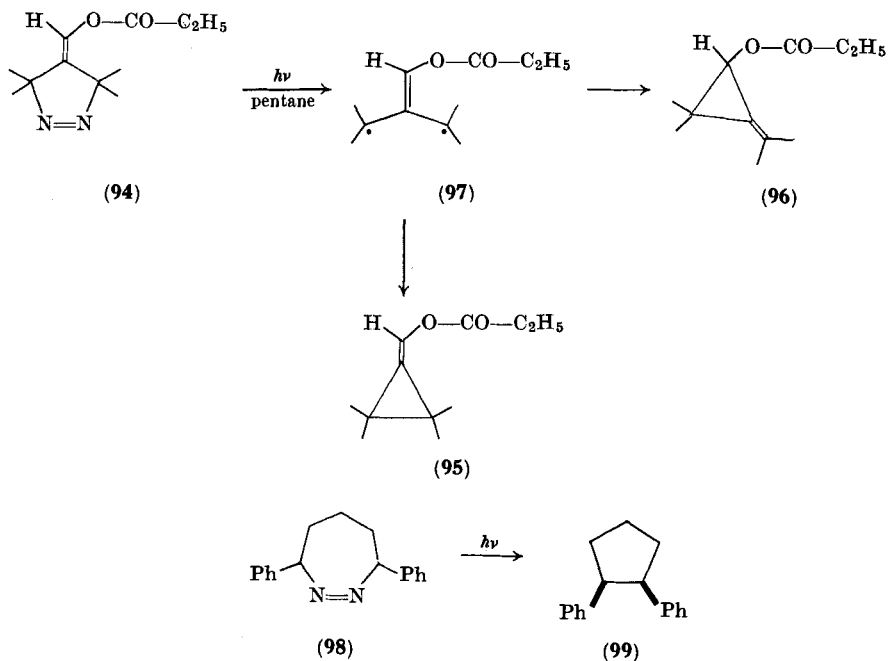
⁷⁶ S. D. Andrews and A. C. Day, *Chem. Commun.* 667 (1966).

⁷⁷ T. Janjiki, H. Kato, and M. Ohta, *Chem. Commun.* 496 (1968).

⁷⁸ P. Dowd, *J. Am. Chem. Soc.* **88**, 2587 (1966).

⁷⁹ C. G. Overberger and C. Yaroslavsky, *Tetrahedron Letters* 4395 (1965).

trans-1,5-diphenylpent-1-ene. Certain phenyl-substituted 1-pyrazolines also show increased stereospecificity on photolysis in the solid state.⁸⁰



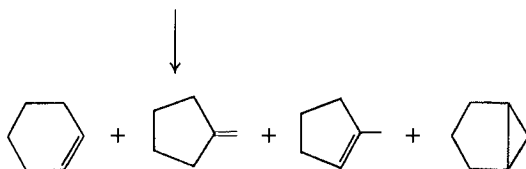
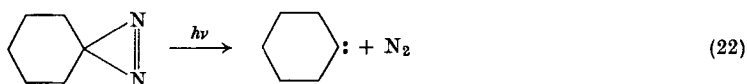
A similar type of photoinduced ring cleavage is reported for diazirines, which have mostly been studied in the gas phase. Diazirine itself in the presence of nitrogen or a hydrocarbon is decomposed to methylene and nitrogen [Eq. (21)], methylene then reacting further with diazirine or with the hydrocarbon.⁸¹ Under the same conditions, methyldiazirine yields ethylene, acetylene, hydrogen, and nitrogen.⁸² A variety of products are formed from disubstituted diazirines. 3,3-Pentamethylenediazirine, for example, is converted into four hydrocarbons, cyclohexene, methylenecyclopentane, 1-methylcyclopent-1-ene, and bicyclo[3.1.0]hexane, and these can be interpreted as arising by an intramolecular process from an intermediate carbene

⁸⁰ C. G. Overberger, N. Weinshenker, and J.-P. Anselme, *J. Am. Chem. Soc.* **87**, 4119 (1965).

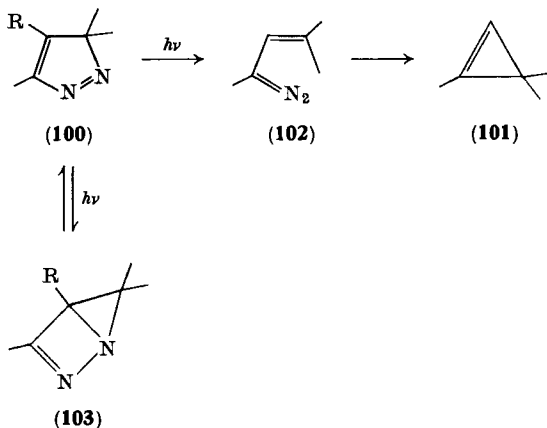
⁸¹ H. M. Frey, *Pure Appl. Chem.* **9**, 527 (1964).

⁸² H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.* 1700 (1965).

[Eq. (22)].⁸³ The addition to olefins of the carbenes generated from 3-bromo-3-phenyldiazirine⁸⁴ and difluoroazirine⁸⁵ has been used as a synthesis of bromophenyl- and difluorocyclopropanes.



The extension of this reaction to include the conversion of 3*H*-pyrazoles into cyclopropenes is established.⁸⁶ 3,3,5-Trimethyl-3*H*-pyrazole (**100**; R = H), for example, on photolysis in pentane solution gives 1,3,3-trimethylcyclopropene (**101**), and an intermediate diazoalkene (**102**) has been characterized. The proposed conversion of the diazoalkene into the cyclopropene (**101**) via a vinylcarbene has a



⁸³ H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.* 4700 (1964).

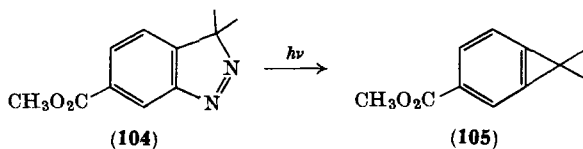
⁸⁴ R. A. Moss, *Tetrahedron Letters* 4905 (1967).

⁸⁵ R. A. Mitsch, *J. Am. Chem. Soc.* **87**, 758 (1965).

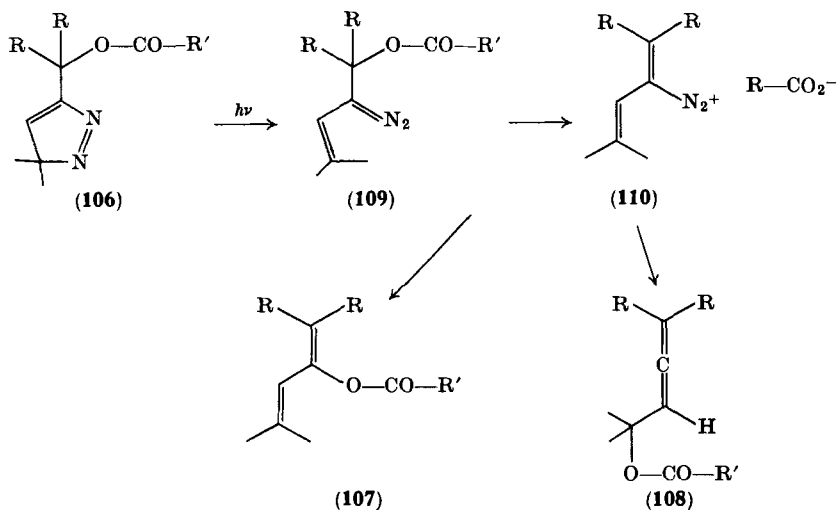
⁸⁶ G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *J. Am. Chem. Soc.* **90**, 173 (1968).

parallel in the previously reported⁸⁷ photocyclization of diazoalkenes to the corresponding cyclopropenes. An interesting example of solvent dependence is observed in this reaction. Fully alkylated 3*H*-pyrazole derivatives such as the tetramethyl-3*H*-pyrazole (**100**; R = CH₃) are photochemically isomerized at -50° in methylene chloride to a species believed to be a 1,2-diazabicyclo[2.1.0]pent-2-ene (**103**); this isomerization is reversible, the 3*H*-pyrazole being regenerated at room temperature. In pentane solution, however, the major product is still the cyclopropene derivative.

The previously unknown benzocyclopropene system was obtained by a similar ring contraction. Photolysis of methyl-3,3-dimethyl-3*H*-indazole-6-carboxylate (**104**) in pentane solution gave the moderately stable methyl-1,1-dimethylbenzocyclopropene-3-carboxylate (**105**).⁸⁸



The 3*H*-pyrazole esters represented by the general formula **106**, in which R and R' are alkyl groups, have been reported⁸⁹ to give, not



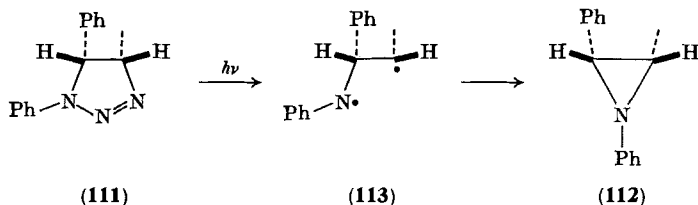
⁸⁷ G. L. Closs, L. E. Closs, and W. A. Böll, *J. Am. Chem. Soc.* **85**, 3796 (1963).

⁸⁸ R. Anet and F. A. L. Anet, *J. Am. Chem. Soc.* **86**, 525 (1964).

⁸⁹ A. C. Day and M. C. Whiting, *J. Chem. Soc. C* 1719 (1966).

cyclopropenes, but a mixture of 1,3-dienes (107) and allenes (108) in the ratio 2:3. The formation of these photoproducts was shown to be intermolecular and involve the diazoester (109), which rapidly rearranges to the isomeric species (110) in preference to loss of nitrogen and carbene formation. The dienes and allenes are then directly formed from 110.

Analogous to the photoreactions of a pyrazoline is the photodecomposition of a 1,2,3-triazoline, which is converted in high yield into an aziridine and nitrogen.⁹⁰ The process is more specific than the corresponding thermal decomposition. Photolysis of *cis*-5-methyl-3,4-diphenyl-1,2,3-triazoline (111) in cyclohexane solution gives predominantly *cis*-3-methyl-1,2-diphenylaziridine (112) and only a little of the *trans* isomer. Retention of configuration is believed to result from a higher rate of cyclization than carbon-carbon bond rotation in the excited singlet state (113). A similar retention is observed for *trans*-triazoline. No appreciable reaction occurs on photolysis in benzene solution,⁹¹ but a sensitized photoreaction does occur in the presence of benzophenone. The formation of the same ratio of *cis*- and *trans*-aziridines from both triazolines is accounted for in terms of a triplet excited state. Other aspects of the mechanism of this reaction have been discussed.⁹⁰



The scope of this reaction has been extended to include a variety of 1,2,3-triazolines [see, for example, Eqs. (23)⁹¹ and (24)⁹²]. The preparation of 2-vinylaziridines from 5-vinyltriazolines has been reported,⁹³ and the synthesis of the first stable benzoazetidine achieved by photolysis of 3-phenyl-4*H*-benzo-1,2,3-triazine [Eq. (25)].⁹⁴

⁹⁰ P. Scheiner, *J. Am. Chem. Soc.* **90**, 988 (1968), and references cited therein.

⁹¹ The triazole has no detectable absorption in the ultraviolet above 335 nm.

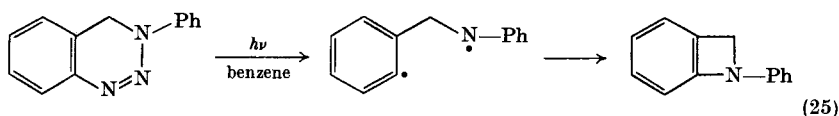
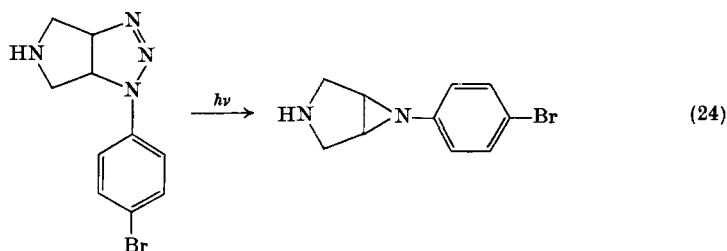
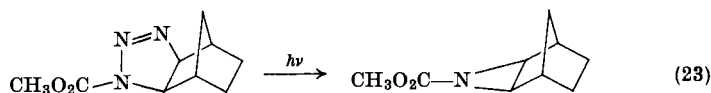
⁹² A. C. Oehlschlager, P. Tillman, and L. H. Zalkow, *Chem. Commun.* 596 (1965).

⁹³ P. Scheiner, *Tetrahedron* **24**, 2757 (1968).

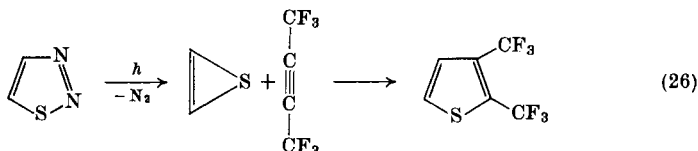
⁹⁴ E. M. Burgess and L. McCullagh, *J. Am. Chem. Soc.* **88**, 1580 (1966).

Irradiation of certain 1-*p*-toluenesulfonate-1,2,3-triazole anions has been employed in the preparation of alkynes.⁹⁵

The photolysis of 1,2,3-thiadiazoles also leads to the evolution of nitrogen, but the unstable thiirene is not obtained. 1,2,3-Thiadiazole itself yields nitrogen, acetylene, and polymer.⁹⁶ In the presence of perfluorobut-2-yne, however, 2,3-bis(trifluoromethyl)thiophene is



obtained, presumably by addition of thiirene to the alkyne [Eq. (26)]. In similar circumstances, 5-methyl-1,2,3-thiadiazole yields only 2,3-bis(trifluoromethyl)-5-methylthiophene. Photolysis of 4,5-diphenyl-1,2,3-thiadiazole, on the other hand, gives⁹⁷ tetraphenyl-1,4-dithiin and the tetraphenyl-2-methylene-1,3-dithiole; the formation of these

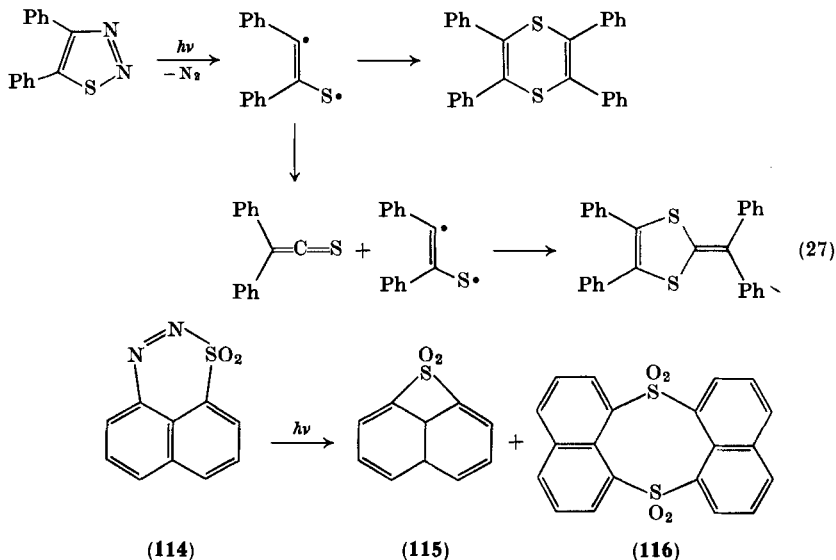


⁹⁵ F. G. Willey, *Angew. Chem. Intern. Ed. Engl.* **3**, 138 (1964).

⁹⁶ O. P. Strausz, J. Font, E. L. Dedio, P. Kebarle, and H. E. Gunning, *J. Am. Chem. Soc.* **89**, 4805 (1967).

⁹⁷ W. Kirmse and L. Horner, *Ann. Chem.* **614**, 4 (1958).

products is rationalized in terms of a diradical intermediate⁹⁷ [Eq. (27)]. Ring closure is observed, however, on photolysis of the thiadiazine 1,1-dioxide (114) in benzene, and the thiete 1,1-dioxide (115) is obtained together with a low yield of the dimer (116).⁹⁸



E. HETEROCYCLIC DIENES

One of the many photoreactions of conjugated dienes is the formation of cyclobutenes,⁹⁹ and this has been reported both in cyclic and acyclic dienes. The stereochemistry of such photocyclizations has been discussed in terms of orbital symmetry by Woodward and Hoffmann.¹⁰⁰

This photoreaction is frequently observed in heterocyclic systems. A number of azacycloheptadienes are photochemically isomerized, in an identical manner to cycloheptadiene itself, to bicyclic derivatives. This is exemplified by the photolysis of 2,3-dihydro-1,3,5,7-tetramethyl-1H-azepine [Eq. (28)],¹⁰¹ and the process has been extended

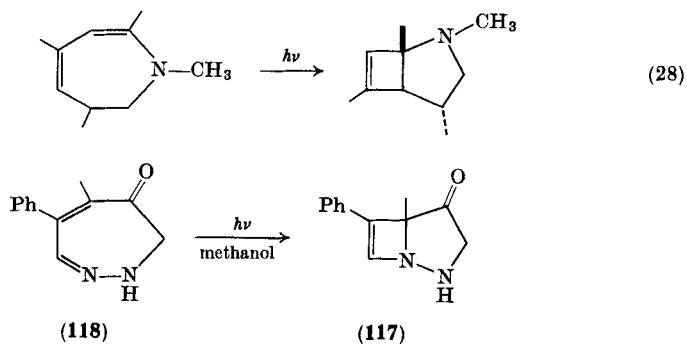
⁹⁸ R. W. Hoffmann and W. Sieber, *Angew. Chem. Intern. Ed. Engl.* **4**, 786 (1965).

⁹⁹ G. J. Fonken, in "Organic Photochemistry" (O. L. Chapman, ed.), Vol. 1, p. 197. Dekker, New York, 1967.

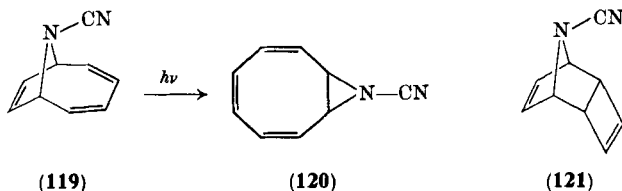
¹⁰⁰ R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965).

¹⁰¹ L. A. Paquette, *Tetrahedron Letters* 2027 (1963).

to include the dihydroazepinone system,¹⁰²⁻¹⁰⁴ and the formation of a 1,2-diazabicyclo[3.2.0]hept-6-en-4-one (**117**) containing a bridge-head nitrogen from the diazepinone (**118**).¹⁰⁵ Photolysis of the corresponding 4-hydroxydiazepine yields a mixture of epimeric alcohols.



The fused dihydroazepine derivative (**119**), however, behaves differently, and undergoes rapid isomerization to 9-cyano-9-azabicyclo[6.1.0]nona-2,4,6-triene (**120**) on photolysis in pentane solution.¹⁰⁶ The mechanism of this reaction is not clear, but the process is thought to be a concerted one, involving a 1,5-migration of the NCN bridge. There is no evidence for the intermediacy of a tricyclic species (such as **121**), but the possibility cannot be excluded.



A bridging reaction, identical to that discussed for dihydroazepines, has been observed in oxygen heterocycles. This was first reported for muconic anhydride¹⁰⁷; more recently, 2,3-dihydrooxepin (**122**) has been converted into 2-oxabicyclo[3.2.0]hept-6-ene (**123**) in 80% yield

¹⁰² O. L. Chapman and E. D. Hoganson, *J. Am. Chem. Soc.* **86**, 498 (1964).

¹⁰³ L. A. Paquette, *J. Am. Chem. Soc.* **86**, 500 (1964).

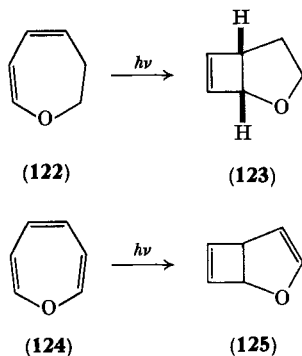
¹⁰⁴ R. F. Childs and A. W. Johnson, *J. Chem. Soc., C* 874 (1967).

¹⁰⁵ W. J. Theuer and J. A. Moore, *Chem. Commun.* 468 (1965).

¹⁰⁶ A. G. Anastassiou and R. P. Cellura, *Chem. Commun.* 762 (1967).

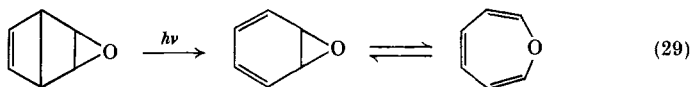
¹⁰⁷ G. J. Fonken, *Chem. & Ind. (London)* 1575 (1961).

by photolysis in ether.¹⁰⁸ Oxepin itself (**124**) is isomerized to the oxabicycloheptadiene (**125**) on irradiation in ether solution, but in acetone solution, phenol is the principal photoproduct.¹⁰⁹ There is an interesting parallel in the photolysis of cycloheptatriene which is converted into bicyclo[3.2.0]hepta-2,6-diene in ether solution¹¹⁰ and into a mixture of this bicycle and toluene in the vapor phase.¹¹¹



Oxepin is obtained by photolysis of the 2,3-oxide of bicyclo[2.2.0]hexa-2,5-diene¹¹² [Eq. (29)]; this process is, in fact, the reverse of the bridging reaction.

The photochemical behavior of cyclohexa-1,3-dienes^{113, 114} differs from that of cycloheptadiene in that another pathway, that of ring opening, is available to the excited molecule in addition to the formation of the bicyclo[2.2.0]hexene system. This is reflected in the behavior of the corresponding heterocyclic derivatives.



1-Methyl-2-pyridone (**126**; $X = N-CH_3$) and 2-pyrone (**126**; $X = O$) are transformed to the corresponding bicyclic system (**127**) by

¹⁰⁸ L. A. Paquette, J. H. Barrett, R. P. Spitz, and R. Pitcher, *J. Am. Chem. Soc.* **87**, 3417 (1965).

¹⁰⁹ J. M. Holovka and P. D. Gardner, *J. Am. Chem. Soc.* **89**, 6370 (1967).

¹¹⁰ W. G. Dauben and R. L. Cargill, *Tetrahedron* **12**, 186 (1961).

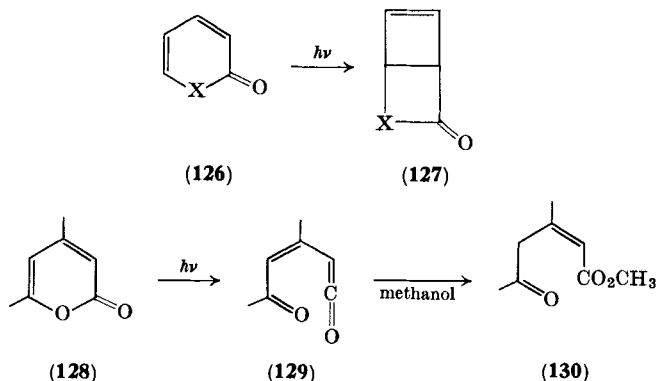
¹¹¹ R. Srinivasan, *J. Am. Chem. Soc.* **84**, 3432 (1962).

¹¹² E. E. van Tamelen and D. Carty, *J. Am. Chem. Soc.* **89**, 3922 (1967).

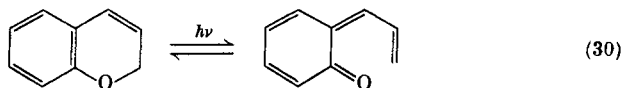
¹¹³ D. H. R. Barton, *Helv. Chim. Acta* **42**, 2604 (1959).

¹¹⁴ R. Srinivasan, *Advan. Photochem.* **4**, 113 (1966).

irradiation in ether,¹¹⁵ and a similar intermediate is postulated in the photolysis of 4,5-diphenyl-2-pyrone.¹¹⁶ 4,6-Dimethyl-2-pyrone (128), however, undergoes ring cleavage on irradiation in methanol,¹¹⁷ presumably via the intermediate ketene (129), to the unsaturated ester (130). Ring cleavage of this type has been proposed to account for



the photochromism of a series of 2*H*-chromenes and 2*H*-pyrans.¹¹⁸ Colorless 2*H*-chromene itself is converted into the colored open-chain form [Eq. (30)] by irradiation at low temperature, and the process is thermally reversible, usually at room temperature. This photoreaction has been observed in a wide variety of naturally occurring 2*H*-pyran derivatives including flindersine (131). It has also previously been



proposed to account for the well-documented¹¹⁹ photochromism of spiropyrans as exemplified by the conversion¹²⁰ of the spiro[indoline-3,2'-pyran] into the colored open-chain compound [Eq. (31)].

An analogous ring cleavage reaction has been reported for unsaturated sultones¹²¹; for example, the sultone (132) is photochemically converted in methanol solution into the methyl sulfonate

¹¹⁵ E. J. Corey and J. Streith, *J. Am. Chem. Soc.* **86**, 950 (1964).

¹¹⁶ A. Padwa and R. Hartman, *J. Am. Chem. Soc.* **86**, 4212 (1964).

¹¹⁷ Reported in P. de Mayo and S. T. Reid, *Quart. Rev. (London)* **15**, 393 (1961).

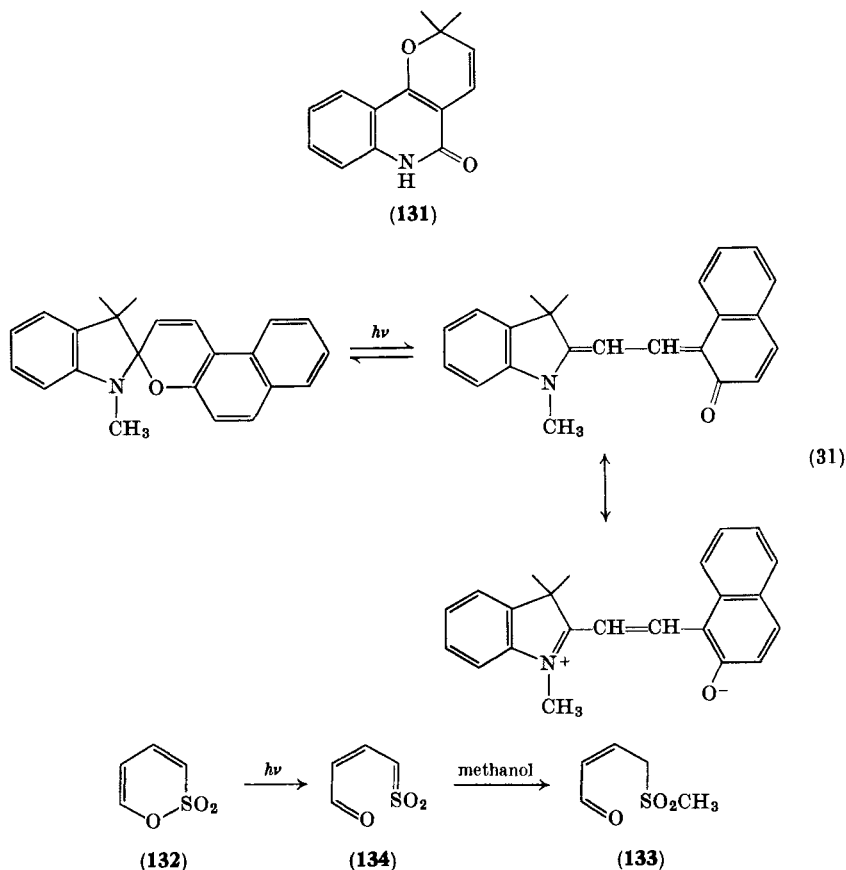
¹¹⁸ R. S. Becker and J. Michl, *J. Am. Chem. Soc.* **88**, 5931 (1966).

¹¹⁹ R. Exelby and R. Grinter, *Chem. Rev.* **65**, 247 (1965).

¹²⁰ R. Heiligman-Rim, Y. Hirshberg, and E. Fischer, *J. Chem. Soc.* 156 (1961).

¹²¹ J. F. King, P. de Mayo, E. Morkved, A. B. M. A. Sattar, and A. Stoessl, *Can. J. Chem.* **41**, 100 (1963).

derivative (133). Recent studies¹²² using flash photolysis have cast doubt on the existence of an intermediate sulfene (134).

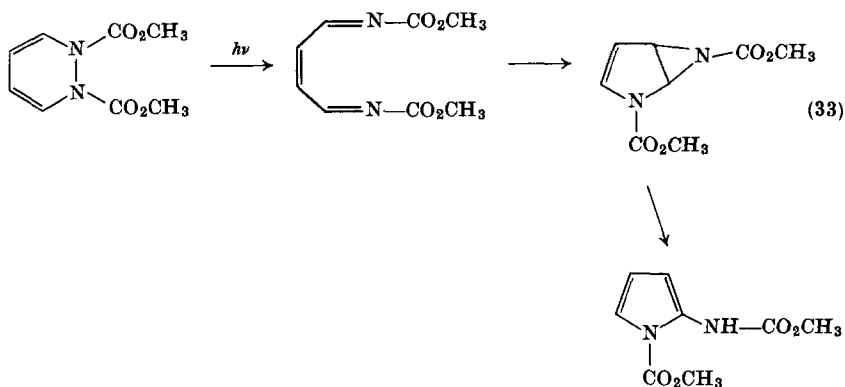
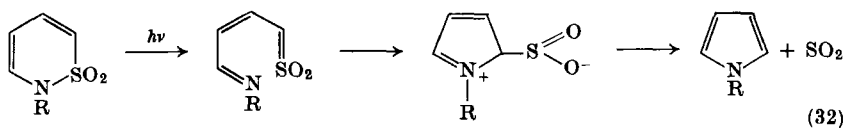


Irradiation of an *N*-substituted sultam yields¹²³ the correspondingly substituted pyrrole; this has been interpreted as arising by nucleophilic attack of nitrogen on an intermediate sulfene [Eq. (32)]. The formation¹²⁴ of a pyrrole by irradiation of dimethyl-1,2-dihydropyridazine-1,2-dicarboxylate in ether is also thought to involve initial ring cleavage [Eq. (33)].

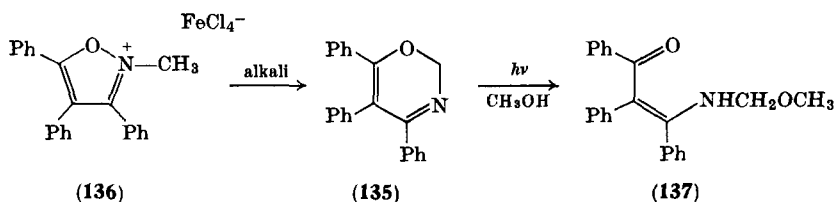
¹²² J. L. Charlton and P. de Mayo, *Can. J. Chem.* **46**, 55 (1968).

¹²³ T. Durst and J. F. King, *Can. J. Chem.* **44**, 1869 (1966).

¹²⁴ L. J. Altman, M. F. Semmelhack, R. B. Hornby, and J. C. Vederas, *Chem. Commun.* **686** (1968).



Ring cleavage of an intermediate oxazine (**135**) by both thermal and photochemical means is postulated to account for the base-catalyzed rearrangement of an *N*-alkyltriphenylisoxazolium salt (**136**) to the acyclic product (**137**).¹²⁵ Other photochemical rearrangements are

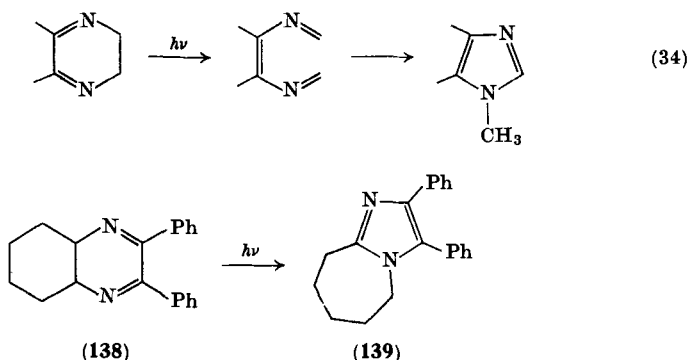


also best interpreted as arising via an initial ring cleavage. In this way, the conversion of 2,3-dihydro-5,6-dimethylpyrazine into 1,4,5-trimethylimidazole in 70% yield by photolysis in ethanol probably involves the intermediate diimine which undergoes rapid cyclization to the imidazole [Eq. (34)].¹²⁶ The reaction can be applied to a variety of dihydropyrazines; the rearrangement of *trans*-2,3-diphenyl-5,6,7,8,9,10-hexahydroquinoxaline (**138**) is accompanied by ring

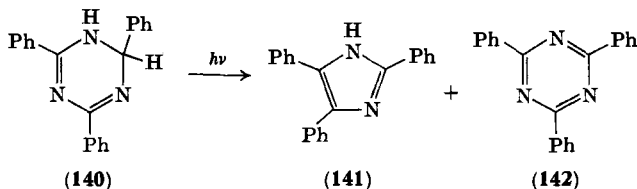
¹²⁵ J. F. King and T. Durst, *Can. J. Chem.* **40**, 882 (1962).

¹²⁶ P. Beak and J. L. Miesel, *J. Am. Chem. Soc.* **89**, 2375 (1967).

enlargement and 2,3-diphenyl-6,7,8,9-tetrahydro-5*H*-imidazo[1,2-*a*]-azepine (**139**) is obtained. Additional products arise both in this and in other cases as a result of oxidation and ethanol incorporation.¹²⁶



The photodecomposition of 1,2-dihydro-2,4,6-triphenyl-*s*-triazine (**140**) in refluxing benzene takes a different course and yields 2,4,5-triphenylimidazole (**141**) and 2,4,6-triphenyl-*s*-triazine (**142**) along with ammonia, toluene, and benzonitrile.¹²⁷ This is believed to be the result of an initial disproportionation reaction yielding hexahydro- and tetrahydro-2,4,6-triphenyl-*s*-triazine.



F. HETEROAROMATIC SYSTEMS

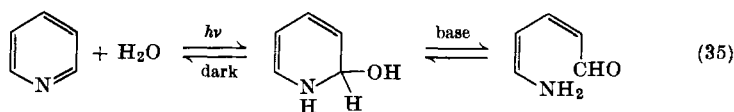
A number of reports of photochemical decomposition of heteroaromatic compounds have appeared in the literature during the past 50 or 60 years. A few of these undoubtedly involve photooxidative processes, whereas others have been examined in the vapor phase, often at elevated temperatures. Recent work includes the study of the photodecomposition of thiophene¹²⁸ and pyrazine.¹²⁹ Furans undergo

¹²⁷ H. L. Nyquist, *J. Org. Chem.* **31**, 784 (1966).

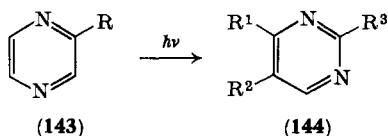
¹²⁸ W. E. Haines, G. L. Cook, and J. S. Ball, *J. Am. Chem. Soc.* **78**, 5213 (1956).

¹²⁹ K. K. Innes, reported in J. G. Calvert and J. N. Pitts, "Photochemistry," p. 460. Wiley, New York, 1966.

a more specific fragmentation process in the vapor phase involving decarbonylation and the formation of the corresponding cyclopropene.¹³⁰ Ring cleavage also occurs in pyridine, but the photochemical step in this case appears to be the photosensitized addition of water to pyridine, rather than direct carbon–nitrogen bond cleavage; an acyclic product is formed when the photolysis is carried out in basic solution [Eq. (35)].¹³¹



Of greater interest, however, is the extent to which the photochemistry of a heteroaromatic system parallels that of benzene and its derivatives. Pyrazine (**143**; R = H) and 2-methylpyrazine (**143**; R = CH₃) undergo photoisomerization both in the vapor phase and in solution with light of 253 nm wavelength to yield pyrimidine (**144**; R₁ = R₂ = R₃ = H), and a mixture of 4-methyl- (**144**; R¹ = CH₃, R² = R³ = H), 5-methyl- (**144**; R² = CH₃, R¹ = R³ = H), and probably 2-methyl-pyrimidine (**144**; R³ = CH₃, R¹ = R² = H), respectively.¹³²



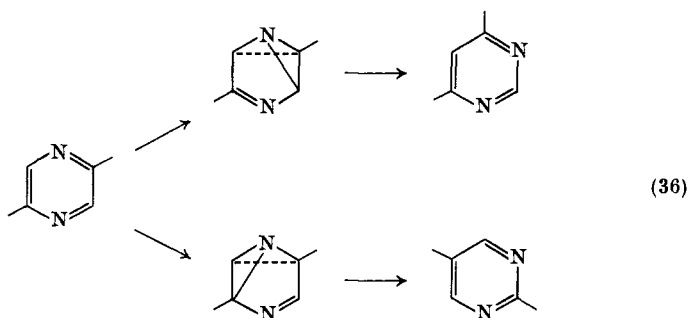
These reactions can be interpreted as proceeding via an intermediate of the diazabenzvalene type, formed from the lowest singlet π , π^* excited state of the pyrazine, and are analogous to the results reported for the photoisomerization of alkylbenzenes.¹³³ Support for this postulate comes from a study of 2,5-dimethylpyrazine which is isomerized to a mixture of 2,5-dimethylpyrimidine and 4,6-dimethylpyrimidine, presumably via the two diazabenzvalenes [Eq. (36)]. There is no evidence for products arising via bicyclohexadiene and prismane intermediates which are also involved in the photo-rearrangement of alkylbenzenes.

¹³⁰ R. Srinivasan, *J. Am. Chem. Soc.* **89**, 1758 (1967).

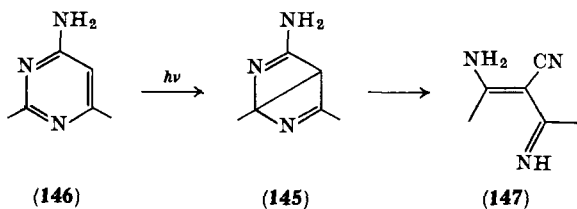
¹³¹ J. Jousset-Dubien and J. Houdard, *Tetrahedron Letters* 4389 (1967).

¹³² F. Lahmani and N. Ivanoff, *Tetrahedron Letters* 3913 (1967).

¹³³ K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.* **87**, 4004 (1965).



A diazabicyclohexadiene (**145**), however, is considered to be an intermediate in the photochemical conversion of 2,6-dimethyl-4-aminopyrimidine (**146**) into the nitrile (**147**).¹³⁴

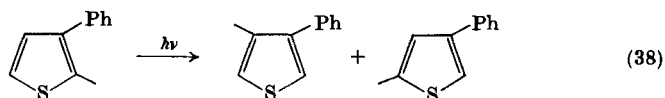
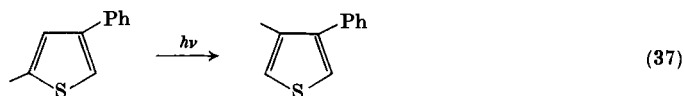
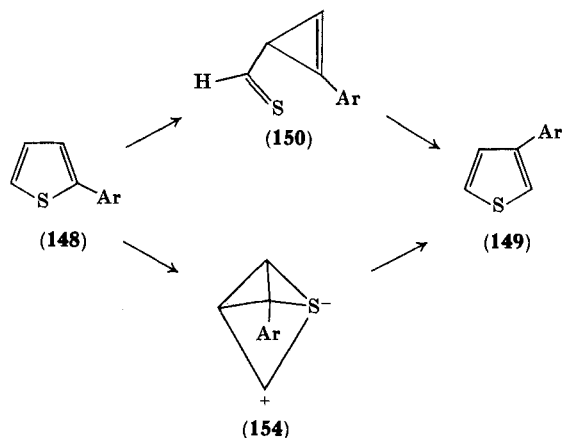


A number of interesting and obviously related rearrangements have been reported for five-membered heterocycles. In particular, a detailed investigation has been made by Wynberg and others¹³⁵ of the photorearrangement of arylthiophenes. 2-Arylthiophenes (**148**) rearrange specifically and irreversibly to 3-arylthiophenes (**149**) by reorganization of the carbon atoms of the thiophene ring involving interchange of the C-2 and C-3 carbon atoms. Methyl- and phenylthiophenes also undergo rearrangement in the manner illustrated [Eqs. (37) and (38)].

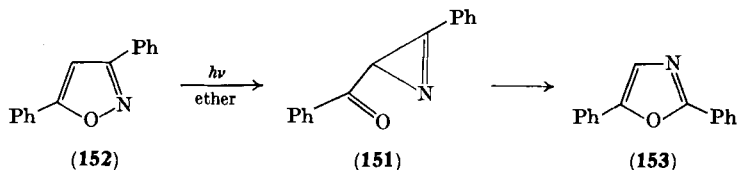
These photoproducts are not now considered to arise from intermediates of the Dewar, prismane, or benzvalene type. The simplest explanation offered is that excitation results in ring cleavage and the formation of a short-lived intermediate (**150**). An analogous inter-

¹³⁴ K. L. Wierzchowski, D. Shugar, and A. R. Katritzky, *J. Am. Chem. Soc.* **85**, 827 (1963).

¹³⁵ H. Wynberg, R. M. Kellog, H. van Driel, and G. E. Beekhuis, *J. Am. Chem. Soc.* **89**, 3501 (1967).



mediate (151) is known to be involved in the rearrangement of 3,5-diphenylisoxazole (152) to 2,5-diphenyloxazole (153),¹³⁶ and in



similar rearrangements of other isoxazoles.^{137, 138} Isolation of the intermediate has finally been achieved in the conversion of 2,5-di-*t*-butylfuran into 2,4-di-*t*-butylfuran [Eq. (39)].¹³⁹

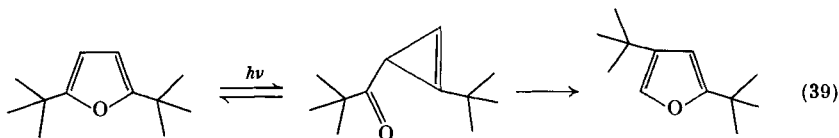
An alternative explanation considered for the thiophene rearrangement is that an intermediate of type 154, arising by expansion of the valence shell of the sulfur atom, may be involved.¹³⁵

¹³⁶ E. F. Ullman and B. Singh, *J. Am. Chem. Soc.* **88**, 1844 (1966).

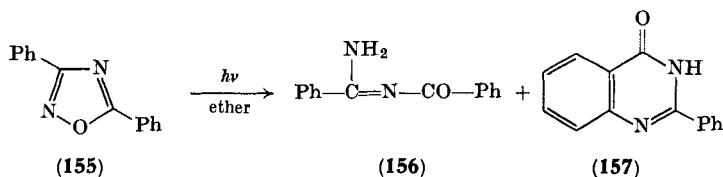
¹³⁷ D. W. Kurtz and H. Shechter, *Chem. Commun.* 689 (1966).

¹³⁸ H. Göth, A. R. Gagneux, C. H. Eugster, and H. Schmid, *Helv. Chim. Acta* **50**, 137 (1967).

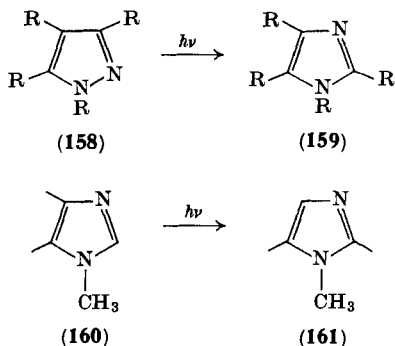
¹³⁹ E. E. van Tamelen and T. H. Whitesides, *J. Am. Chem. Soc.* **90**, 3894 (1968).



It is interesting to note that 3,5-diphenyl-1,2,4-oxadiazole (**155**) undergoes a slow ring cleavage on irradiation in ether, giving benzoylbenzamidine (**156**) and 2-phenyl-4-quinazolone (**157**) as major products.¹⁴⁰ Ring cleavage also occurs in 1,2,5-oxadiazoles, 1,2,5-thiadiazoles, and 2*H*-1,2,3-triazoles.¹⁴¹



Photorearrangement has been observed in certain pyrazoles. *N*- and *C*-alkylated pyrazoles (**158**) are converted into imidazoles (**159**) by interchange of the N-2 and C-3 atoms.¹⁴² 1,4,5-Trimethylimidazole (**160**) itself undergoes rearrangement to the alternative 1,2,5-trimethylimidazole (**161**),¹⁴³ presumably by a different pathway.



Two processes are available¹⁴² to the corresponding indazole; *N*-1-alkylated indazoles [Eq. (40)], afford 2-alkylaminobenzonitriles

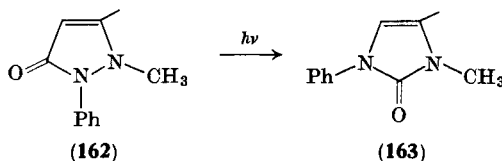
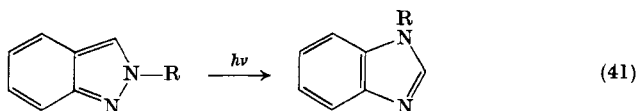
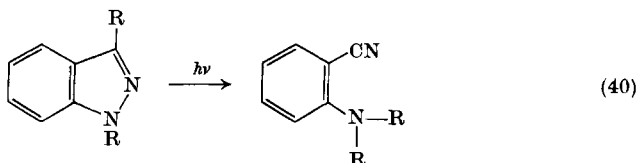
¹⁴⁰ H. Newman, *Tetrahedron Letters* 2417 (1968).

¹⁴¹ T. S. Cantrell and W. S. Haller, *Chem. Commun.* 977 (1968).

¹⁴² H. Tiefenthaler, W. Dörscheln, H. Göth, and H. Schmid, *Helv. Chim. Acta*, **50**, 2244 (1967).

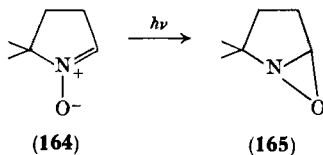
¹⁴³ P. Beak, J. L. Miesel, and W. R. Messer, *Tetrahedron Letters* 5315 (1967).

by ring cleavage [Eq. (40)], whereas *N*-2-alkylated indazoles rearrange in good yield to the *N*-1-alkylated benzimidazoles [Eq. (41)]. A surprisingly similar reaction is observed¹⁴⁴ in the pyrazolone anti-pyrine (**162**) which on irradiation in methanol is initially converted into the imidazolinone (**163**); ring cleavage products are also isolated.



G. NITRONES AND HETEROAROMATIC *N*-OXIDES

Simple nonconjugated nitrones have a strong absorption maximum in the UV at around 230 nm. Acyclic nitrones are, in general, photochemically cyclized to the corresponding oxaziridines.¹⁴⁵ The cyclic nitrone, 5,5-dimethyl-1-pyrroline 1-oxide (**164**) is similarly converted into the oxaziridine (**165**) by photolysis in ethanol/cyclohexane solution,¹⁴⁶ and several 2-substituted 1-pyrroline 1-oxides were subsequently found to undergo the same cyclization in cyclohexane solution.¹⁴⁷



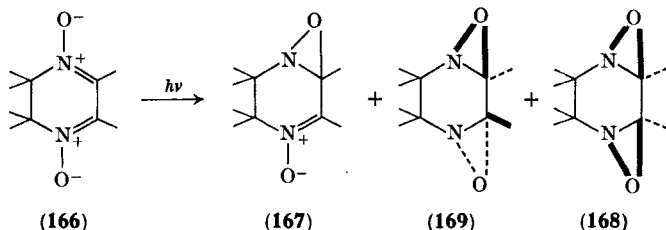
¹⁴⁴ S. N. Ege, *Chem. Commun.* 488 (1967).

¹⁴⁵ J. S. Splitter and M. Calvin, *J. Org. Chem.* **30**, 3427 (1965).

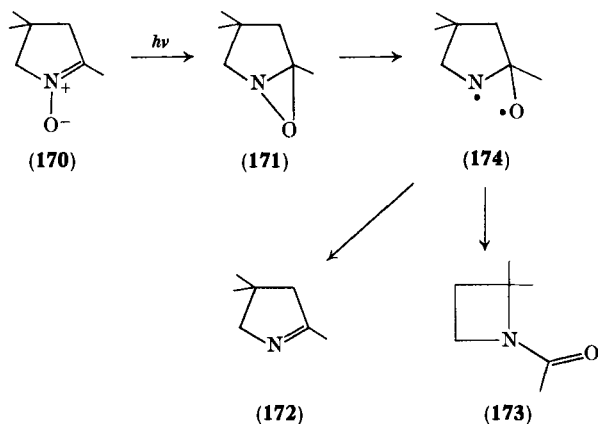
¹⁴⁶ R. Bonnett, V. M. Clark, and Sir A. Todd, *J. Chem. Soc.* 2102 (1959).

¹⁴⁷ L. S. Kaminsky and M. Lamchen, *J. Chem. Soc., C* 2295 (1966).

Although hexamethyl-2,3-dihydropyrazine 1,4-dioxide (166) does not exhibit typical nitron properties, oxaziridines are nevertheless formed on photolysis; with light of wavelength greater than 300 nm, only the monooxaziridine (167) is formed, whereas with light of wavelength down to 200 nm, *cis*- (168) and *trans*- (169) dioxaziridines are obtained.¹⁴⁸



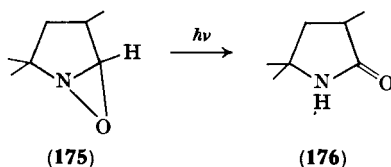
Prolonged irradiation of nitrones in ethanol, however, leads to the formation of other products, arising presumably from the oxaziridine. Both 2,4,4-trimethyl-1-pyrroline 1-oxide (170) and the corresponding oxaziridine (171) are, for example, converted in this way into 2,4,4-trimethyl-1-pyrroline (172) and the *N*-acetylazetidine (173); these products are both believed to arise from the common intermediate 174, formed by cleavage of the nitrogen-oxygen bond of the oxaziridine. The greater ease of formation of this oxaziridine in cyclohexane solution has been attributed¹⁴⁷ to a shift in the UV absorption maximum from 229 nm in ethanol to 242 nm in cyclohexane, and to



¹⁴⁸ M. Lamchen and T. W. Mittag, *J. Chem. Soc., C* 1917 (1968).

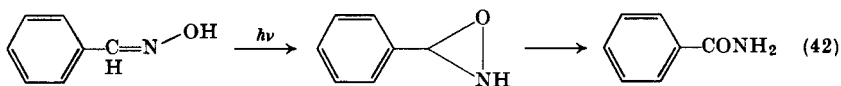
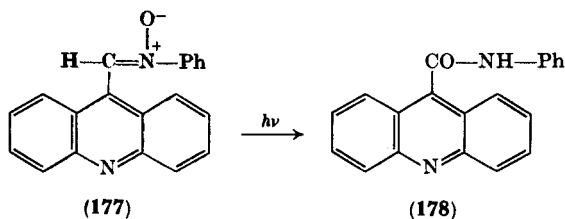
the ability of cyclohexane to act as a filter solution, absorbing light of less than 200 nm which might be expected to induce photocleavage of the oxaziridine.

The principal product of prolonged irradiation of the oxaziridine (175), formed from 3,5,5-trimethyl-1-pyrroline 1-oxide, is 3,5,5-trimethyl-2-pyrrolidone (176). In this instance, the 1,2-shift of a hydrogen atom, possible in pyrrolidines not containing an alkyl substituent on C-2, is preferable to pyrrolidine ring cleavage. A similar effect is observed in the photolysis of 5,5-dimethyl-1-pyrroline 1-oxide.¹⁴⁷



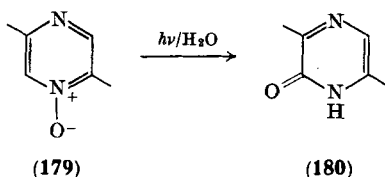
A transformation of this type also occurs in the photochemical rearrangement of the acyclic nitron (177) to the amide (178) and an intermediate oxaziridine may be involved in the photochemical conversion¹⁴⁹ of aryl oximes into the corresponding amides [Eq. (42)].

The heteroaromatic *N*-oxides have been the subject of more recent investigation. The structure of the photoproduct appears to be dependent on a number of factors including the nature of the heterocycle and its substituents, and the solvent employed in the photolysis. The product can almost always be interpreted as arising via an intermediate unstable oxaziridine, but in no instance has this been isolated.

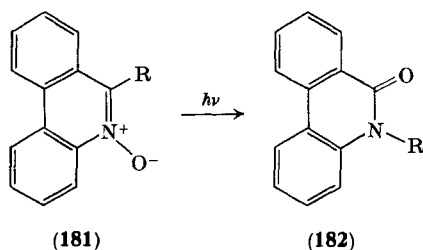


¹⁴⁹ J. H. Amin and P. de Mayo, *Tetrahedron Letters* 1585 (1963).

Certain aromatic *N*-oxides undergo rearrangement by a process equivalent to that observed in nitrones to give the corresponding lactam. This is illustrated by the conversion of 2,5-dimethylpyrazine 1-oxide (**179**) into the lactam (**180**) by photolysis in aqueous solution.¹⁵⁰



Similar transformations have been reported for quinoline 1-oxide and 3-, 4-, 5-, 6-, 7-, and 8-methylquinoline 1-oxides in aqueous solution,¹⁵¹ for quinoxaline 1-oxide,¹⁵² for adenine 1-oxide,¹⁵³ and for phenanthridine 5-oxide (**181**; R = H) which yields phenanthridone (**182**; R = H).¹⁵⁴



In 6-methyl- and 6-phenylphenanthridine 5-oxide (**181**; R = CH₃, Ph), rearrangement of the intermediate oxaziridine is accompanied by methyl or phenyl migration, and 5-methyl- and 5-phenyl-6-(5*H*)-phenanthridinones (**182**; R = CH₃, Ph) are isolated in high yield on irradiation in ethanol.¹⁵⁵ In benzene solution, however, the photolysis is more complex,¹⁵⁶ and the principal products of irradiation of 6-phenylphenanthridine 5-oxide are 2-benzamido-2'-hydroxybiphenyl, 6-phenylphenanthridine, and 5-phenyl-6-(5*H*)-phenanthridone.

¹⁵⁰ N. Ikekawa and Y. Honma, *Tetrahedron Letters* 1197 (1967).

¹⁵¹ O. Buchardt, J. Becher, and C. Lohse, *Acta Chem. Scand.* **19**, 1120 (1965).

¹⁵² J. K. Landquist, *J. Chem. Soc.* 2830 (1953).

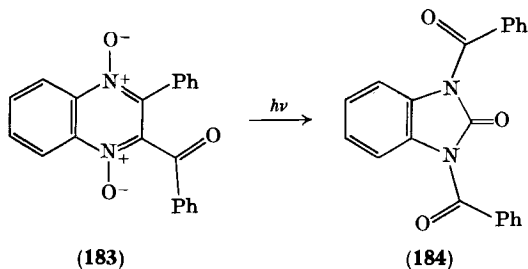
¹⁵³ G. B. Brown, G. Levin, and S. Murphy, *Biochemistry* **3**, 880 (1964).

¹⁵⁴ M. Ishikawa, S. Yamada, H. Hotta, and C. Kaneko, *Chem. Pharm. Bull. (Tokyo)* **14**, 1102 (1966).

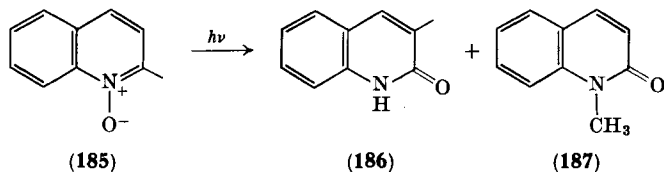
¹⁵⁵ E. C. Taylor and G. G. Spence, *Chem. Commun.* 767 (1966).

¹⁵⁶ E. C. Taylor and G. G. Spence, *Chem. Commun.* 1037 (1968).

Migration accompanying the cleavage of an oxaziridine is also involved in the rearrangement in high yield of 2-benzoyl-3-phenylquinoxaline 1,4-dioxide (**183**) to the benzimidazolone (**184**) on photolysis in methanol.¹⁵⁷



The photolysis of 2-methylquinoline 1-oxide (**185**) in aqueous or methanolic solution is equally interesting; it affords 3-methyl- (**186**) and 1-methylquinolin-2-one (**187**).¹⁵⁴



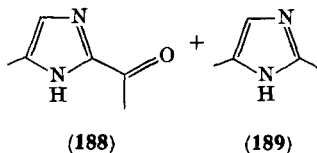
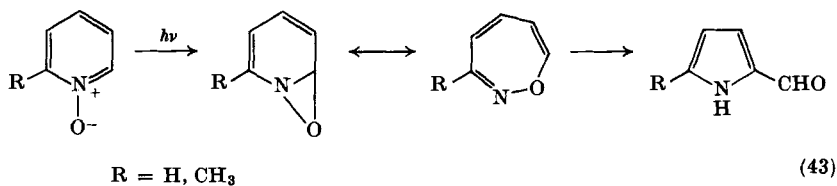
The observed photochemical ring contraction of monocyclic aromatic *N*-oxides can also be interpreted as proceeding through an intermediate oxazirane. Pyridine 1-oxide and 2-methylpyridine 1-oxide are transformed in low yield to pyrrole-2-aldehyde and 2-methylpyrrole-2-aldehyde [Eq. (43)], respectively, by photolysis in an inert solvent.¹⁵⁸ In ethanol solution, additional products are formed.¹⁵⁹ 2,5-Dimethylpyrazine 1-oxide (**179**) affords the two possible imidazole derivatives (**188** and **189**) on irradiation in benzene solution, whereas the pyrazinone (**180**) is obtained in aqueous solution.¹⁶⁰ This solvent dependence may well be explained by the more ready heterolytic cleavage of the nitrogen-oxygen bond in polar solvents. Certain pyridazine *N*-oxides also undergo ring contraction to the corresponding pyrazole.¹⁶⁰

¹⁵⁷ M. J. Haddadin and C. H. Issidorides, *Tetrahedron Letters* 753 (1967).

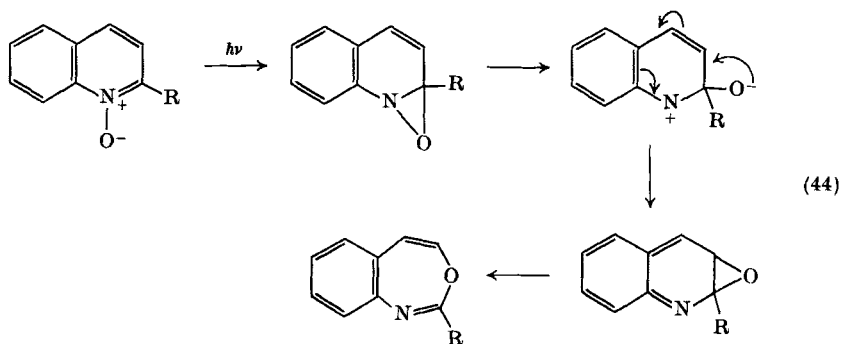
¹⁵⁸ J. Streith and C. Sigwalt, *Tetrahedron Letters* 1347 (1966).

¹⁵⁹ A. Alkaitis and M. Calvin, *Chem. Commun.* 292 (1968).

¹⁶⁰ M. Ogata and K. Kano, *Chem. Commun.* 1176 (1967).



Heteroaromatic *N*-oxides are also frequently observed to undergo ring expansion with the formation of oxazepines. Photolyses in benzene¹⁶¹ or acetone¹⁶² of a series of 2-substituted quinoline 1-oxides yield, as the principal product, the substituted benz[*d*]-1,3-oxazepine; for example, both 2-phenylquinoline 1-oxide and 2-cyanoquinoline 1-oxide are converted into the corresponding oxazepine [Eq. (44)] in high yield. An oxaziridine is again believed to be an intermediate in this reaction sequence, but the precise mechanism of the rearrangement of the oxaziridine to the oxazepine is not clear. It must, however, involve initial cleavage of the nitrogen–oxygen bond

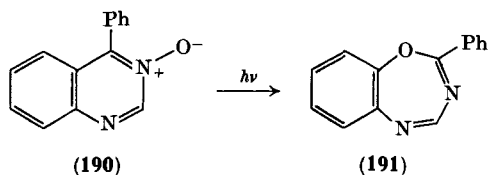


followed by bond formation between C-3 and the oxygen atom. This has been represented¹⁶² in ionic terms, but could equally well be considered as a radical process.

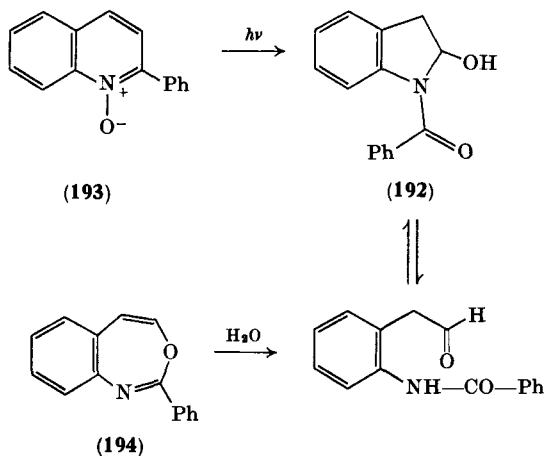
¹⁶¹ S. Yamada, I. Yokoe, and M. Ishikawa, *Tetrahedron Letters* 1873 (1967).

¹⁶² O. Buchardt, B. Jensen, and I. Kjoller Larsen, *Acta Chem. Scand.* **21**, 1841 (1967).

Ring expansion has also been observed in the transformation of certain 1-cyano- and 1-phenylisoquinoline 2-oxides to the corresponding benz[*f*]-1,3-oxazepines,¹⁶³ of phenyl-substituted quinoxaline 1-oxides to the substituted benz[*d*]-1,3,6-oxadiazepines,^{161,164} and of 4-phenylquinazoline 3-oxide (190) to 2-phenylbenz[*f*]-1,3,5-oxadiazepine (191).¹⁶⁵



N-Benzoyl-2-hydroxy-2,3-dihydroindoles (192) are additional products resulting from the photolysis of 2-phenylquinoline 1-oxide (193) and its derivatives in ethanol solution.¹⁶² These dihydroindoles are also formed by the solvolysis of the corresponding benz[*d*]-1,3-oxazepines (194) with aqueous ethanol at room temperature, and are therefore interpreted as arising in this way in the photolysis. Quinoline 1-oxide itself undergoes ring contraction¹⁶⁶ to *N*-formyl-2-hydroxy-2,3-dihydroindole on irradiation in a protonic solvent.



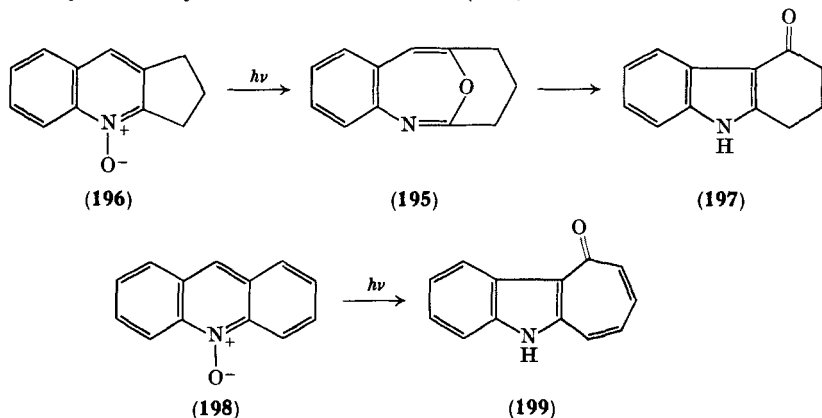
¹⁶³ O. Buchardt, C. Lohse, A. M. Duffield, and C. Djerassi, *Tetrahedron Letters* 2741 (1967).

¹⁶⁴ O. Buchardt and J. Feeney, *Acta Chem. Scand.* **21**, 1399 (1967).

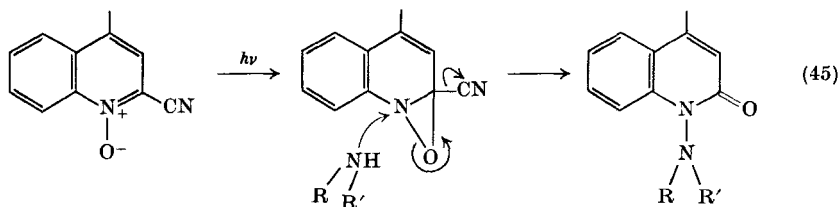
¹⁶⁵ C. Kaneko and S. Yamada, *Tetrahedron Letters* 5233 (1967).

¹⁶⁶ J. Streith, H. K. Darrah, and M. Weil, *Tetrahedron Letters* 5555 (1966).

An intermediate oxazepine (**195**) has also been postulated to account for the ring contraction of 2,3-trimethylenequinoline 1-oxide (**196**) to 4-oxo-1,2,3,4-tetrahydrocarbazole (**197**) on irradiation.¹⁶⁷ The intermediate oxazepine has been isolated in the analogous conversion of 1,2,3,4-tetrahydroacridine 10-oxide,¹⁶⁷ but acridine 10-oxide (**198**) itself yields only the indole derivative (**199**).¹⁶⁸



A number of other miscellaneous transformations of hetero-aromatic *N*-oxides have been reported. Of particular interest is the application¹⁶⁹ of the photolysis of 2-cyanoquinoline 1-oxides to the synthesis of 1-aminocarbostyrils; 2-cyano-4-methylquinoline 1-oxide is converted into the quinolinone by irradiation in dichloromethane solution in the presence of a secondary amine, and the conversion presumably takes place via the intermediate oxaziridine [Eq. (45)].



Photolysis of 1,4-diphenylphthalazine 2-oxide (**200**) in acetone yields 1,3-diphenylisobenzofuran (**201**), and this is interpreted as arising by loss of nitrogen from the intermediate oxaziridine (**202**).¹⁷⁰

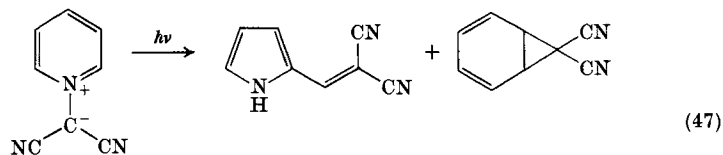
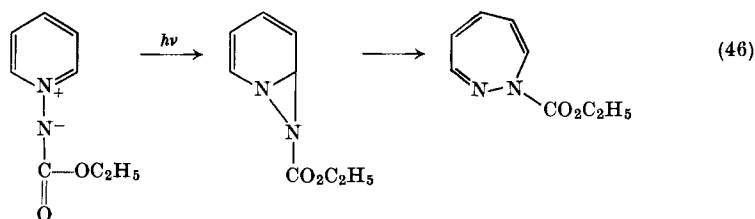
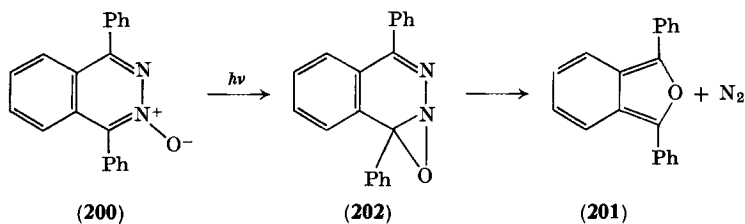
¹⁶⁷ S. Yamada, I. Yokoe, and M. Ishikawa, *Tetrahedron Letters* 1873 (1967).

¹⁶⁸ M. Ishikawa, C. Kaneko, and S. Yamada, *Tetrahedron Letters* 4519 (1968).

¹⁶⁹ C. Kaneko, I. Yokoe, and M. Ishikawa, *Tetrahedron Letters* 5237 (1967).

¹⁷⁰ O. Buchardt, *Tetrahedron Letters* 1911 (1968).

Other processes that occur to a minor extent in the photolysis of heteroaromatic *N*-oxides are deoxygenation and solvent incorporation.¹⁶⁰ A few photoreactions, which are obviously related to those described above for heteroaromatic *N*-oxides, have been reported. These include the photolysis^{171, 172} of certain pyridinium ylides to give 1*H*-1,2-diazepine derivatives [Eq. (46)], and the photolysis¹⁷¹ of pyridinium dicyanomethide [Eq. (47)].



IV. Photoaddition to Heterocycles

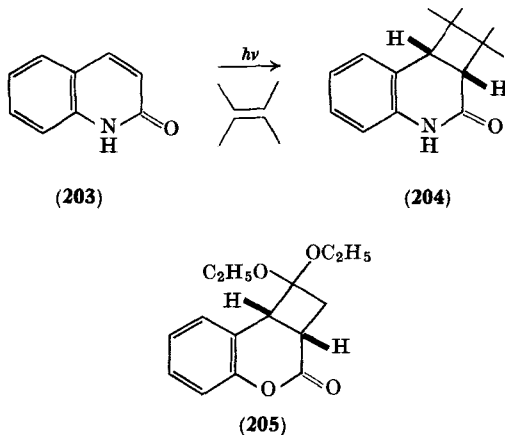
Photoaddition to heterocyclic systems occurs both as a result of excitation of the heterocycle or of the species undergoing addition. Dimerization will be discussed separately.

¹⁷¹ J. Streith, A. Blind, J. M. Cassal, and C. Sigwalt, *Bull. Soc. Chim. France* 948 (1969).

¹⁷² T. Sasaki, K. Kanematsu, and A. Kakehi, *Chem. Commun.* 432 (1969).

A. 1,2-CYCLOADDITION

Cycloaddition, analogous in many respects to the dimerization of heterocycles, is frequently observed. Photochemical excitation of quinolin-2-one (**203**) in the presence of tetramethylethylene in ethanol solution leads to the formation in good yield of the 1,1-adduct (**204**), in addition to the dimer of quinolin-2-one.¹⁷³ Similar cycloadditions have been reported with isobutylene, cyclopentene, and vinyl methyl ether.¹⁷³ Coumarin, on the other hand, undergoes efficient photosensitized addition to tetramethylethylene, cyclopentene, and ketene diethyl acetal¹⁷⁴; the structure of the adduct (**205**) with ketene diethyl acetal is in agreement with the recent postulate¹⁷⁵ that the geometry of the addition is controlled by an intermediate π complex, formed between the excited state of one molecule and the ground state of another. Other factors appear to be implicated in determining the structure of a cycloadduct.¹⁷⁶ The structures of the photoadducts of coumarin with indene¹⁷⁷ and with 2-chloroindene¹⁷⁸ have been elucidated, and analogous cycloadditions of indene and ethyl vinyl ether to certain furocoumarins have been reported.¹⁷⁹



¹⁷³ G. R. Evanega and D. L. Fabiny, *Tetrahedron Letters* 2241 (1968).

¹⁷⁴ J. W. Hanifin and E. Cohen, *Tetrahedron Letters* 1419 (1966).

¹⁷⁵ E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Am. Chem. Soc.* **86**, 5570 (1964).

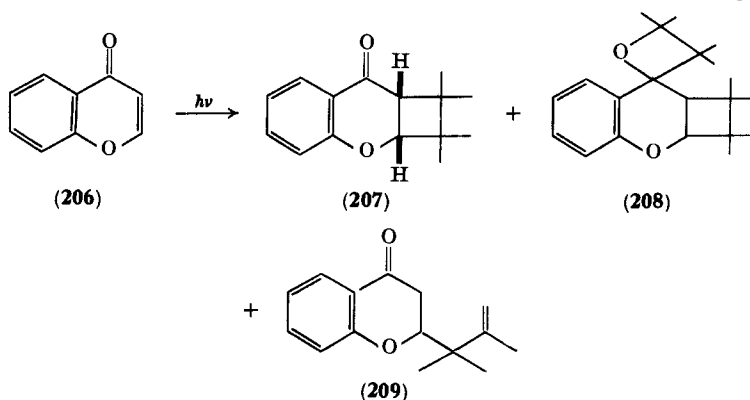
¹⁷⁶ B. D. Challand and P. de Mayo, *Chem. Commun.* 982 (1968).

¹⁷⁷ J. Bowyer and Q. N. Porter, *Australian J. Chem.* **19**, 1455 (1966).

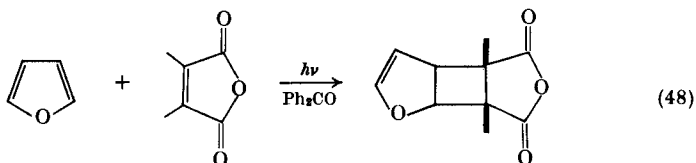
¹⁷⁸ C. H. Krauch and W. Metzner, *Chem. Ber.* **99**, 88 (1966).

¹⁷⁹ C. H. Krauch and S. Farid, *Chem. Ber.* **100**, 1685 (1967).

Unlike coumarin, chromone (206) undergoes efficient unsensitized photoaddition to tetramethylethylene, cyclopentene, ketene dimethyl acetal, and but-2-yne.¹⁸⁰ The major product of such an addition to tetramethylethylene is the *cis*-fused cyclobutane derivative (207); the formation of the two minor products (208 and 209) is easily rationalized. Added benzophenone has no visible effect on this cycloaddition, which is therefore believed to involve the attack of triplet chromone on the ground-state alkene. Photoaddition to furochromones has also been studied,¹⁷⁹ and the photosensitized cyclo-



additions of dimethylmaleic anhydride to furan itself¹⁸¹ [Eq. (48)], to thiophene,¹⁸² and to 1,3-diacetylimidazolin-2-one¹⁸³ have been



reported. Two products, the 2,1-adduct and the 1,1-adduct, are formed by the unsensitized photoaddition of dimethylacetylene dicarboxylate to furan [Eq. (49)],¹⁸⁴ and diphenylacetylene undergoes 1,2-cycloaddition to 2,3-dihdropyran.¹⁸⁵

¹⁸⁰ J. W. Hanifin and E. Cohen, *Tetrahedron Letters* 5421 (1966).

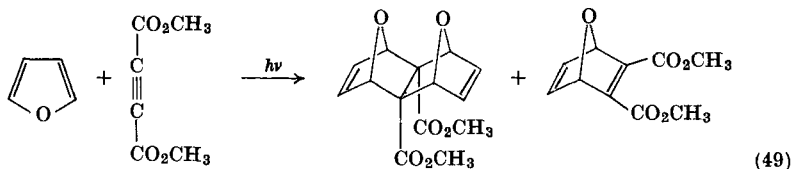
¹⁸¹ G. O. Schenck, W. Hartmann, S.-P. Mannsfeld, W. Metzner, and C. H. Krauch, *Chem. Ber.* **95**, 1642 (1962).

¹⁸² G. O. Schenck, W. Hartmann, and R. Steinmetz, *Chem. Ber.* **96**, 498 (1963).

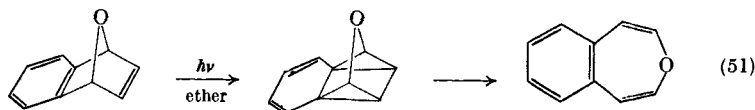
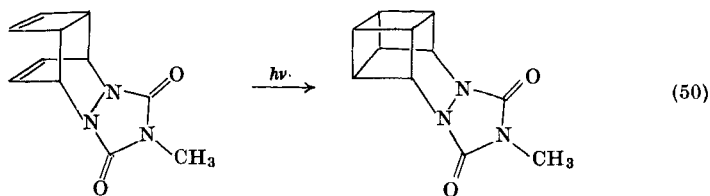
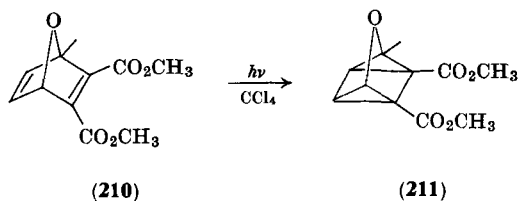
¹⁸³ G. Steffan and G. O. Schenck, *Chem. Ber.* **100**, 3961 (1967).

¹⁸⁴ R. P. Gandhi and V. K. Chadha, *Chem. Commun.* 552 (1968).

¹⁸⁵ H. M. Rosenberg and P. Serve, *J. Org. Chem.* **33**, 1653 (1968).



The related oxobicyclic (**210**), on photolysis in carbon tetrachloride, is converted into the isomer (**211**) in high yield by an intramolecular cycloaddition.¹⁸⁶ The same transformation has been observed in norbornadiene, and other intramolecular cycloadditions are known [see, for example, Eq. (50)¹⁸⁷]. An intermediate of this type has been postulated¹⁸⁸ to account for the photorearrangement of 1,4-epoxy-1,4-dihydronaphthalene to benz[*f*]oxepin [Eq. (51)].



The tetrahydro-2-quinolone (**212**) affords a very small yield of 1,2-cycloadduct on irradiation with diphenylacetylene in methanol.¹⁸⁹ The two major products are the 1,4-dimer and the pentacyclic derivative (**213**), arising presumably by intramolecular photocycloaddition

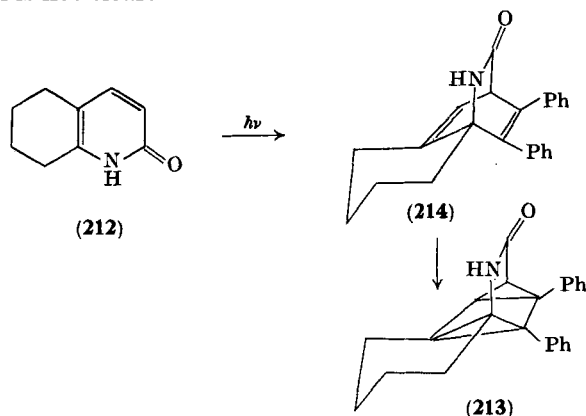
¹⁸⁶ E. Payo, L. Cortés, J. Mantecón, C. Rivas, and G. de Pinto, *Tetrahedron Letters* 2415 (1967).

¹⁸⁷ C. M. Anderson, J. B. Bremner, I. W. McCay, and R. N. Warrener, *Tetrahedron Letters* 1255 (1968).

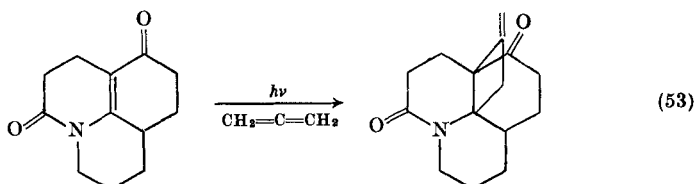
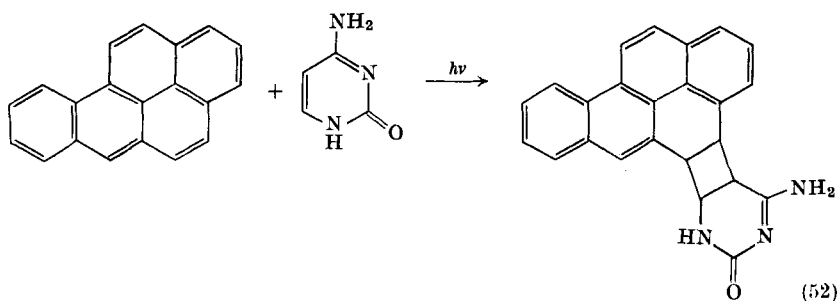
¹⁸⁸ G. R. Ziegler and G. S. Hammond, *J. Am. Chem. Soc.* **90**, 513 (1968).

¹⁸⁹ A. I. Meyers and P. Singh, *Tetrahedron Letters* 4073 (1968).

of the 1,4-cycloadduct (**214**).¹⁹⁰ Further irradiation of **213** in benzene also yields the 1,2-cycloadduct, but the mechanism of this transformation is not clear.



Other cycloadditions of interest include the photoaddition [Eq. (52)] of pyrimidine derivatives such as cytosine to the carcinogenic hydrocarbon benzo[*a*]pyrene,¹⁹¹ and the photoaddition of allene as a vital step [Eq. (53)] in the synthesis of an annottinine derivative.¹⁹²

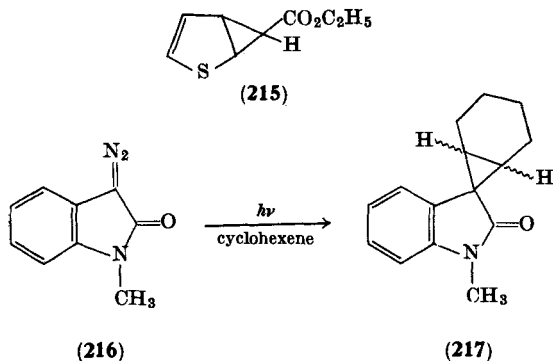


¹⁹⁰ A. I. Meyers and P. Singh, *Chem. Commun.* 576 (1968).

¹⁹¹ J. M. Rice, *J. Am. Chem. Soc.* **86**, 1444 (1964).

¹⁹² K. Wiesner, I. Jirkovský, M. Fishman, and C. A. J. Williams, *Tetrahedron Letters* 1523 (1967).

The formation of cyclopropane derivatives by photolysis of diazoalkanes in the presence of alkenes is believed to occur by photolytic decomposition of the diazoalkane to yield the carbene, followed by addition of this carbene to the alkene. Cycloaddition of this type has been reported in furan, dihydrofuran, and thiophene.¹⁹³ Thus, photolysis of ethyl diazoacetate in thiophene yields the bicyclic sulfur heterocycle (215). Alternatively, photolysis of 3-diazo-1-methyloxindole (216) in cyclohexene leads to the formation of two isomers which are thought to have the spirocyclopropyl structure (217); photolysis in ethanol yields 3-ethoxy-1-methyloxindole.¹⁹⁴



B. MISCELLANEOUS PHOTOADDITIONS

The alkylation of saturated oxygen heterocycles such as tetrahydrofuran, tetrahydropyran, and dioxane with alkenes by photolysis in the presence of acetone has been reported.^{195, 196} Such alkylations occur on the carbon atom adjacent to the oxygen atom; the mechanism of formation is thought to involve initial hydrogen abstraction from this position by excited acetone, followed by addition of the resultant radical to the alkene. This is illustrated for tetrahydropyran in Eq. (54). Improved yields are obtained with diethyl maleate and diethyl fumarate. In the absence of alkenes, the two radicals formed by hydrogen abstraction can recombine to give, in some cases, good yields of the tertiary alcohol¹⁹⁷ [see, for example, Eq. (55)].

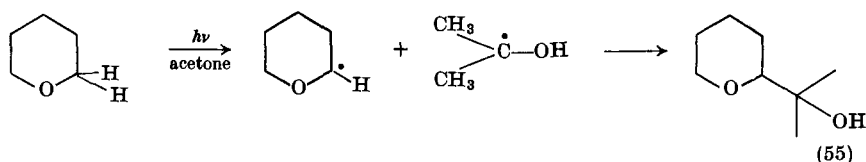
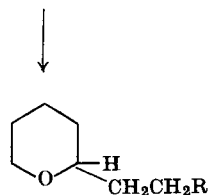
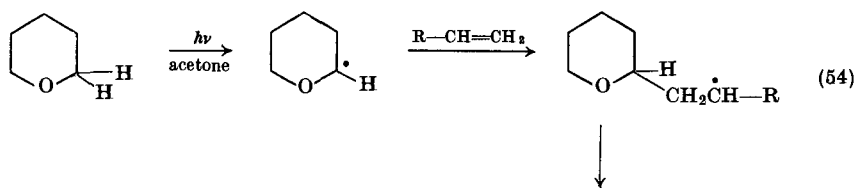
¹⁹³ G. O. Schenck and R. Steinmetz, *Ann. Chem.* **668**, 19 (1963).

¹⁹⁴ E. J. Moriconi and J. J. Murray, *J. Org. Chem.* **29**, 3577 (1964).

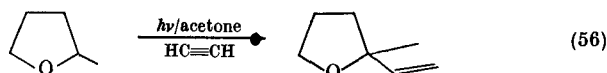
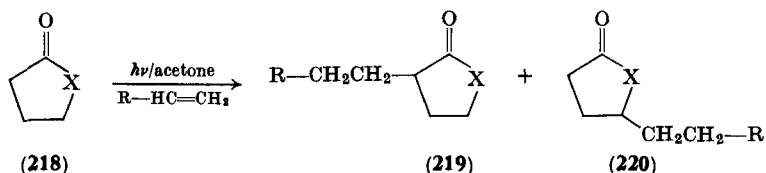
¹⁹⁵ I. Rosenthal and D. Elad, *Tetrahedron* **23**, 3193 (1967).

¹⁹⁶ D. Elad and R. D. Youssefeyeh, *J. Org. Chem.* **29**, 2031 (1964).

¹⁹⁷ K. Shima and S. Tsutsumi, *Bull. Chem. Soc. Japan* **36**, 121 (1963).



A similar alkylation of acetals has been reported,^{198,199} while 2-pyrrolidone²⁰⁰ (**218**; X = NH) and γ -butyrolactone²⁰¹ (**218**; X = O) are also alkylated under identical conditions to give a major (**219**) and a minor (**220**) photoproduct. The addition of 2-methyltetrahydrofuran to acetylene [Eq. (56)] is also initiated by photolysis in acetone.²⁰²



A parallel reaction is observed with diethyl azodicarboxylate which on photolysis in dioxane yields²⁰³ the adduct (**221**).

¹⁹⁸ I. Rosenthal and D. Elad, *J. Org. Chem.* **33**, 805 (1968).

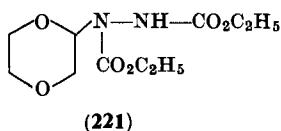
¹⁹⁹ In the absence of alkenes, acetals are converted into esters by ring cleavage on photolysis in acetone; D. Elad and R. D. Youssefyeh, *Tetrahedron Letters* 2189 (1963).

²⁰⁰ D. Elad and J. Sinnreich, *Chem. & Ind., (London)* 768 (1965).

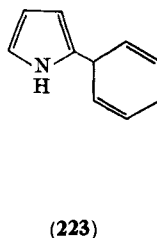
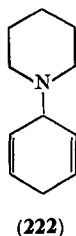
²⁰¹ D. Elad, G. Friedman, and R. D. Youssefyeh, *J. Chem. Soc., C* 870 (1968).

²⁰² R. Srinivasan and K. H. Carlough, *Can. J. Chem.* **45**, 3209 (1967).

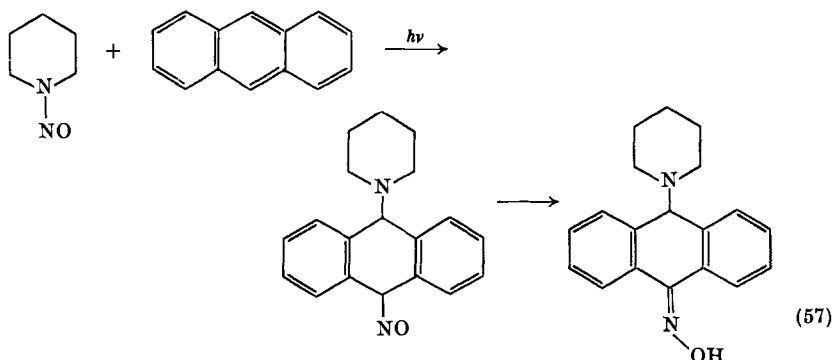
²⁰³ R. C. Cookson, I. D. R. Stevens, and C. T. Watts, *Chem. Commun.* 259 (1965).



The 1,4-addition of heterocycles to aromatic systems has been reported. Photolysis of piperidine in benzene, for example, leads to the formation of the *N*-substituted piperidine (222).²⁰⁴ Pyrrole, on photolysis in benzene, behaves differently and yields the 2-substituted pyrrole (223).²⁰⁵ In both instances, excitation of benzene, probably to the triplet, appears to be the initial step in the photolysis. The photolysis of *N*-nitrosopiperidine in the presence of anthracene also results in 1,4-addition and the formation of an anthrone oxime,



presumably via the *C*-nitroso compound [Eq. (57)].²⁰⁶ The photo-reaction of *N*-nitrosoamines with alkenes is known,²⁰⁷ and yields the 1,2-adduct [Eq. (58)].

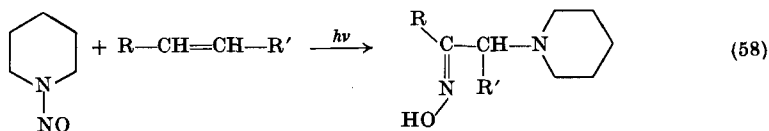


²⁰⁴ M. Bellas, D. Bryce-Smith, and A. Gilbert, *Chem. Commun.* 862 (1967).

²⁰⁵ M. Bellas, D. Bryce-Smith, and A. Gilbert, *Chem. Commun.* 263 (1967).

²⁰⁶ Y. L. Chow, *Chem. Commun.* 330 (1967).

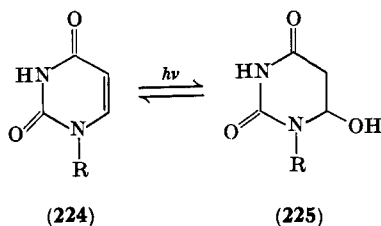
²⁰⁷ Y. L. Chow, *Can. J. Chem.* **43**, 2711 (1965).



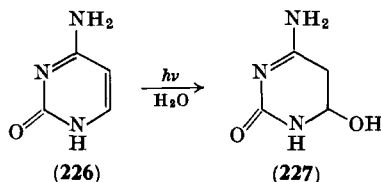
C. ADDITION OF WATER OR AN ALCOHOL

Photoadditions of water and primary alcohols to unsaturated bonds have been reported, but insufficient compounds have been studied to allow any generalizations to be made.

The photoaddition of water to a variety of naturally occurring pyrimidine derivatives has been reported. Photolysis in aqueous solution of uracil (**224**; R = H), uridine (**224**; R = ribosyl), and uridylic acid results in the formation of the corresponding 6-hydroxy-5,6-dihydropyrimidine (**225**)²⁰⁸⁻²¹⁰; these structures have been established by independent synthesis.²⁰⁹ Analogous photoadditions have been observed in 1,3-dimethyluracil²¹¹ and 5-fluorouracil.²¹² These additions are reversible.



The aminopyrimidine derivatives, cytosine (**226**), cytidine, and cytidylic acid, form unstable adducts (**227**), with water; these are



²⁰⁸ R. W. Chambers, *J. Am. Chem. Soc.* **90**, 2192 (1968).

²⁰⁹ E. Fahr, *Angew. Chem. Intern. Ed. Engl.* **7**, 551 (1968).

²¹⁰ S. I. Miller and R. U. Cerutti, *Proc. Natl. Acad. Sci. U.S.A.* **59**, 34 (1968).

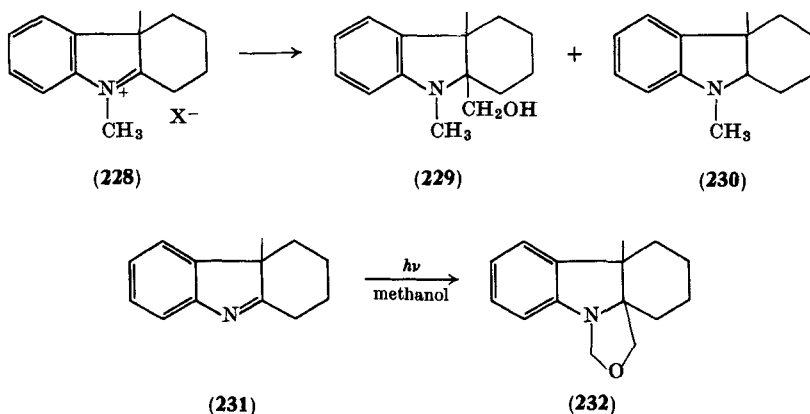
²¹¹ S. Y. Wang, M. A. Apicella, and B. R. Stone, *J. Am. Chem. Soc.* **78**, 4180 (1956).

²¹² H. A. Lozeron, M. P. Gordon, T. Gabriel, W. Tautz, and R. Duschinsky, *Biochemistry* **3**, 1844 (1964).

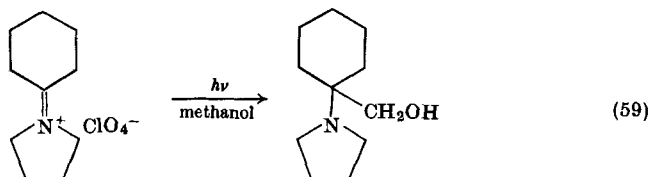
readily converted into the related 6-hydroxyuracil derivatives by a dark reaction.^{209, 213} These additions are believed to be implicated in the photochemistry of deoxyribonucleic acid (DNA).

The photoaddition of water to the ergot alkaloids has been the subject of a number of studies,^{214, 215} and the structures of the adducts have been elucidated.

The unsaturated quaternary salt (228) undergoes photolysis in methanol to give the adduct (229), together with a small amount of the reduction product (230).²¹⁶ The corresponding free base (231), however, is converted in good yield into the adduct (232) by a process that must involve oxidation.



The benzophenone-sensitized addition of methanol to cyclohexylidenepyrrolidinium perchlorate [Eq. (59)] and other iminium salts has also been observed,²¹⁷ whereas 1-methyl-3,4-dihydroisoquinoline [Eq. (60)] and *N*-methylbenzalimine both yield a *cis*- and



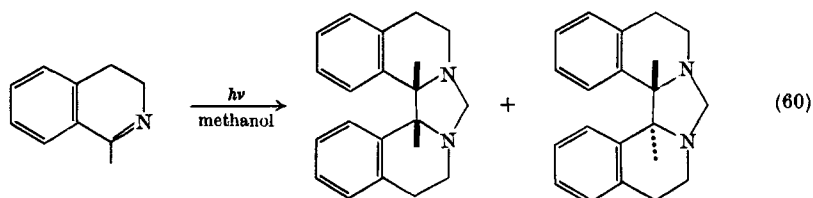
²¹³ K. L. Wierzchowski and D. Shugar, *Photochem. Photobiol.* **1**, 21 (1962).

²¹⁴ A. Stoll and W. Schlienz, *Helv. Chim. Acta* **38**, 585 (1955).

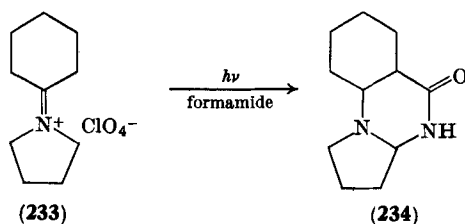
²¹⁵ H. Hellberg, *Acta Chem. Scand.* **11**, 219 (1957); **16**, 1363 (1962).

²¹⁶ P. Cerutti and H. Schmid, *Helv. Chim. Acta* **45**, 1992 (1962).

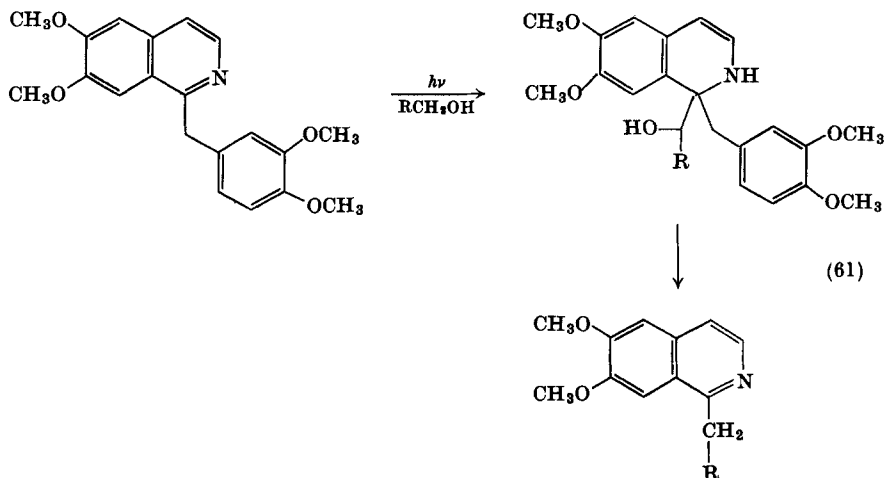
²¹⁷ W. Dörscheln, H. Tiefenthaler, H. Göth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta* **50**, 1759 (1967).



trans-imidazolidine.²¹⁸ The product of photoaddition of formamide to 1-cyclohexylidenepyrrrolidinium perchlorate (**233**) is the imidazolidinone (**234**).



Photoinduced addition of methanol or ethanol is postulated to account for the conversion of papaverine into 1-methyl- or 1-ethyl-6,7-dimethoxyisoquinoline²¹⁹ [Eq. (61)]. The alkylation of phen-



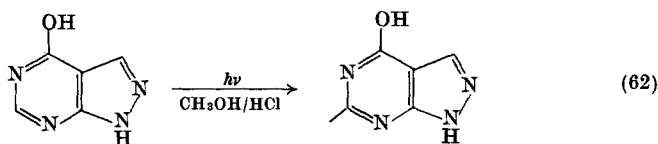
²¹⁸ P. Cerutti and H. Schmid, *Helv. Chim. Acta* **47**, 203 (1964).

²¹⁹ F. R. Stermitz, R. P. Seiber, and D. E. Nicodem, *J. Org. Chem.* **33**, 1136 (1968).

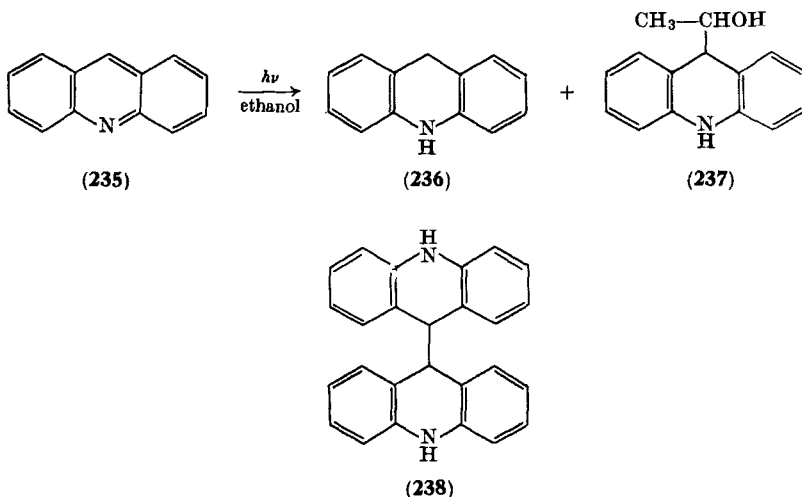
anthridine to give 6-ethylphenanthridine,²¹⁹ and the photomethylation of a series of pyrimidine and condensed pyrimidine derivatives²²⁰ [see, for example, Eq. (62)] can be similarly rationalized. The photoaddition of alcohols to purine has also been reported.²²¹

The first step in all these photoadditions must be hydrogen abstraction from the alcohol by the excited molecule; this is then followed either by radical recombination to yield the substituted alcohol or further hydrogen abstraction to give the dihydro compound.

The equivalent 1,4-addition is reported^{222, 223} in acridine (**235**) and its quaternary salt on irradiation in ethanol. Both acridan (**236**) and the alcohol (**237**) are formed in low yield, and the major product is 9,9'-diacridan (**238**). A similar process is reported in methanol²²²;



in dioxane and cyclohexane solution,²²³ 9-dioxanylacridan and 9-cyclohexylacridan are also formed.



²²⁰ M. Ochiai and K. Morita, *Tetrahedron Letters* 2349 (1967).

²²¹ H. Linschitz and J. S. Connolly, *J. Am. Chem. Soc.* **90**, 2979 (1968).

²²² H. Göth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta* **48**, 1395 (1965).

²²³ F. Mader and V. Zanker, *Chem. Ber.* **97**, 2418 (1964).

D. DIMERIZATION OF HETEROCYCLES

Photochemically induced dimerization²²⁴ readily occurs both in the solid state and in concentrated solution, and is, in general, the result of the intermolecular addition of an excited molecule to a second molecule in the ground state. Intramolecular reactions compete with dimerization in more dilute solution.

1. 1,2-Cycloaddition: Cyclobutane Formation

The most commonly observed dimerization is that of alkenes to form cyclobutane derivatives. Nonconjugated alkenes such as cyclopentene and norbornene are dimerized in the presence of a sensitizer, whereas conjugated alkenes dimerize directly; dimerizations of the second type have been observed in dienes, phenylethylenes, and α,β -unsaturated carbonyl, cyano, and nitro derivatives. The precise structure and stereochemistry of many of these dimers is uncertain, although it is known to be influenced by the solvent, by the presence and nature of substituents, and by the use of a sensitizer. The structures of dimers formed in solid-state irradiations are often determined by crystal structure.

Dimerizations of alkenes bearing heteroaromatic substituents such as pyridine have been widely reported. 2-(β -Styryl)quinoline (**239**), for example, yields on irradiation in the solid state a dimer which can be represented either as the head-to-head dimer (**240**) or the head-to-tail dimer (**241**).²²⁵ The stereochemistry of ring fusion in this and many other related dimers is not known. The structures of the dimers obtained by solid state photolysis of β -2-furyl-, β -2-thienyl-, and β -3-pyridylacrylic acid have been interpreted in terms of crystal packing.²²⁶

Dimerizations have, in addition, been reported in heterocyclic systems containing an exocyclic carbon-carbon double bond. The pseudooxazolone (**242**) is, in this way, converted into the dimer (**243**),²²⁷ and a similar transformation has been observed on irradiation of 3-benzilidene phthalide.²²⁸

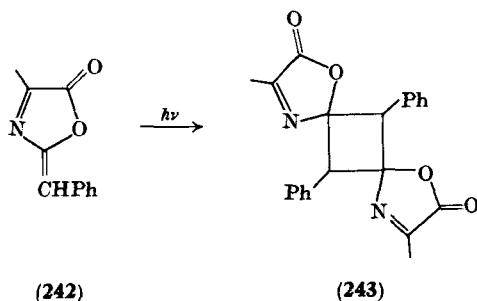
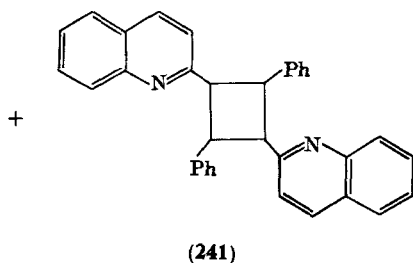
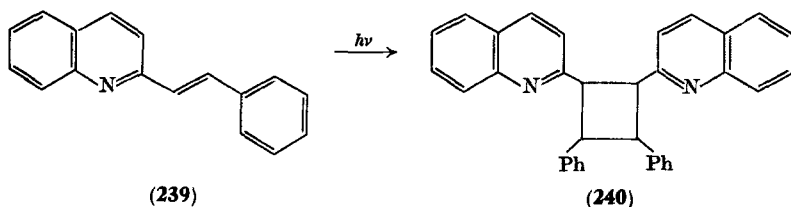
²²⁴ For a recent discussion of dimerization, see R. O. Kan, "Organic Photochemistry," p. 155. McGraw-Hill, New York, 1966.

²²⁵ M. Henze, *Chem. Ber.* **70**, 1273 (1937).

²²⁶ M. Lahav and G. M. J. Schmidt, *J. Chem. Soc., B* 239 (1967).

²²⁷ R. Filler and E. J. Piasek, *J. Org. Chem.* **28**, 221 (1963).

²²⁸ M. J. Jorgenson, *J. Org. Chem.* **28**, 2929 (1963).

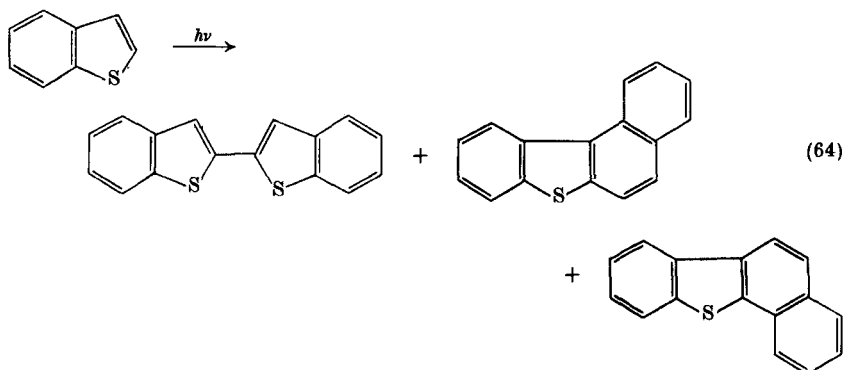
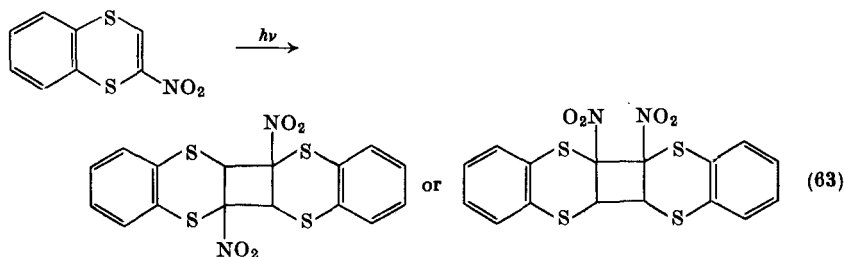


Of considerably greater interest in the present context are the dimerizations occurring between actual heterocyclic systems. Both 2-nitrobenzo-1,4-dithiin²²⁹ [Eq. (63)] and benzo[*b*]thiophene 1,1-dioxide²³⁰ undergo dimerization, although, once again, it is not possible to decide between the head-to-head or head-to-tail structure on the basis of the available evidence. Benzo[*b*]thiophene itself behaves quite differently on irradiation, and undergoes dehydrogenation and loss of hydrogen sulfide [Eq. (64)].²³¹

²²⁹ W. E. Parham, P. L. Stright, and W. R. Hasek, *J. Org. Chem.* **24**, 262 (1959).

²³⁰ W. Davies and F. C. James, *J. Chem. Soc.* 314 (1955); A. Mustafa and S. M. A. D. Zayed, *J. Am. Chem. Soc.* **78**, 6174 (1956).

²³¹ W. E. Haines, G. L. Cook, and J. S. Ball, *J. Am. Chem. Soc.* **78**, 5213 (1956).



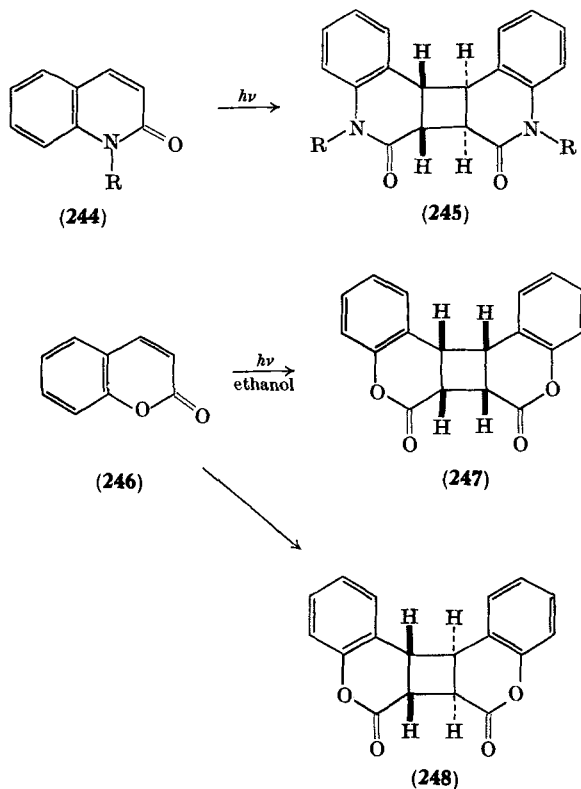
The photoproducts obtained from quinolin-2-one (**244**; R = H) and its *N*-methyl derivative (**244**; R = CH₃) have been examined in greater detail, and have been found to have the *trans* head-to-head structure (**245**).²³² A study of the oxygen analog, coumarin (**246**), provides further evidence concerning the mechanism of such dimerizations.²³³ Direct photolysis in ethanol²³³ or other polar solvents²³⁴ yields the *cis* head-to-head dimer (**247**), whereas the formation of *trans* head-to-head dimer (**248**) is favored in nonpolar solvents and in photolyses sensitized by benzophenone. There appears to be general agreement²³³⁻²³⁵ that the *trans* dimer (**248**) is formed from a monomeric excited triplet, and that the *cis* dimer (**247**) arises either through singlet coumarin or a singlet excimer of coumarin. Two other dimers of coumarin, the *cis* and *trans* head-to-tail adducts, have also been characterized.

²³² O. Buchardt, *Acta Chem. Scand.* **18**, 1389 (1964).

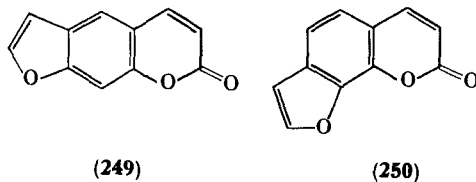
²³³ G. S. Hammond, C. A. Stout, and A. A. Lamola, *J. Am. Chem. Soc.* **86**, 3103 (1964).

²³⁴ H. Morrison, H. Curtis, and T. McDowell, *J. Am. Chem. Soc.* **88**, 5415 (1966).

²³⁵ C. H. Krauch, S. Farid, and G. O. Schenck, *Chem. Ber.* **99**, 624 (1966).



Umbelliferone (7-hydroxycoumarin) readily dimerizes in sunlight,²³⁶ and certain naturally occurring furocoumarins have been photochemically dimerized in the laboratory. These include psoralen (249), bergapten (5-methoxypsoralen), angelicin²³⁷ (250), and peucedanin.²³⁸ The corresponding dimer of xanthotoxin (8-methoxypsoralen) could not be obtained under identical conditions, but on

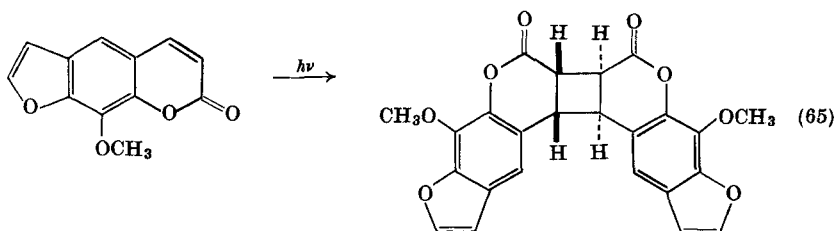


²³⁶ F. V. Wessely and I. Plaichinger, *Chem. Ber.* **75**, 971 (1942).

²³⁷ G. Rodighiero and V. Cappellina, *Gazz. Chim. Ital.* **91**, 103 (1961).

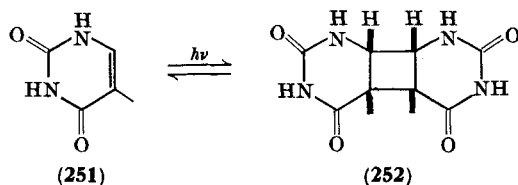
²³⁸ G. K. Nikonov, *J. Gen. Chem. USSR (English Transl.)* **34**, 2848 (1964).

irradiation in dioxane solution, a product believed to be the *trans* head-to-head dimer was isolated²³⁹ [Eq. (65)]. Some of these furocoumarins have a photosensitizing action on the skin of man, the most active being psoralen.²⁴⁰⁻²⁴² The presence of bergapten and oxy-peucedanin in vegetables is undoubtedly responsible for the development of certain types of photodermatitis. There is, however, no direct correlation between the ease of photochemical dimerization and



photosensitizing activity²³⁷ and, in fact, the dimer of psoralen is inactive as a skin-photosensitizing agent. A photoreaction between furocoumarin and flavinmononucleotide has been observed²⁴³ and subsequent work has demonstrated that a photoreaction also takes place between pyrimidine bases²⁴⁴ and DNA²⁴⁵ and the skin-active furocoumarin. It is at least possible that a photoaddition of this type is responsible for the biological effects of the furocoumarins.

Another dimerization of some biological significance is that of thymine. The major product of irradiation of thymine (**251**) with UV light (254 nm) in frozen aqueous solution is a dimer²⁴⁶ to which the



²³⁹ C. H. Krauch and S. Farid, *Chem. Ber.* **100**, 1685 (1967).

²⁴⁰ L. Musajo, G. Rodighiero, and G. Caporale, *Bull. Soc. Chim. Biol.* **36**, 1213 (1954).

²⁴¹ L. Musajo and G. Rodighiero, *Experientia* **18**, 153 (1962).

²⁴² L. Musajo, *Pure Appl. Chem.* **6**, 369 (1963).

²⁴³ L. Musajo and G. Rodighiero, *Nature* **190**, 1109 (1961).

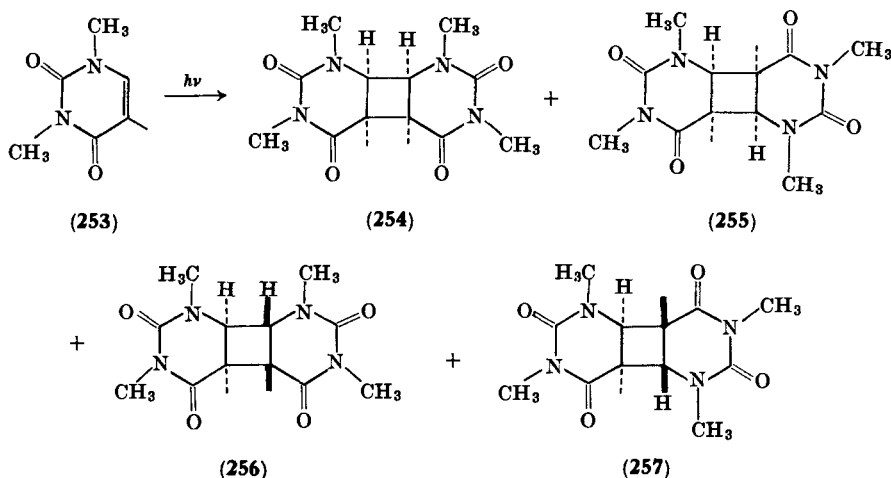
²⁴⁴ L. Musajo, F. Bordin, and R. Bevilacqua, *Photochem. Photobiol.* **6**, 927 (1967).

²⁴⁵ L. Musajo, G. Rodighiero, A. Breccia, F. Dall'acqua, and G. Malfsani, *Experientia* **22**, 75 (1966); *Photochem. Photobiol.* **5**, 739 (1966).

²⁴⁶ R. Beukers and W. Berends, *Biochim. Biophys. Acta* **41**, 550 (1960).

structure **252** can be assigned on the basis of chemical²⁴⁷ and spectroscopic²⁴⁸ evidence. The same dimer is also obtained by irradiation of crystalline thymine on filter paper,²⁴⁹ but the process is reversed in aqueous solution at room temperature and the dimer is reconverted to thymine with the same light source. This reversibility has also been observed in the photodimerization^{249, 250} of 1,3-dimethylthymine and of uracil, and a slower rate of dimerization has been observed for 5-hydroxymethyluracil.²⁵¹

The same thymine dimer has been obtained indirectly from thymidylyl-(3',5')-thymidine,²⁵² and has been isolated from DNA by hydrolysis after irradiation with UV light both *in vivo*²⁵³ and *in vitro*.²⁵⁴ The identity of this dimer has recently been confirmed chemically.²⁵⁵ This dimerization between two adjacent thymine residues is thought to be one of the major factors responsible for the photochemical inactivation of transforming DNA. There are conflicting views as to whether the dimerization occurs within one strand or



²⁴⁷ G. M. Blackburn and R. J. M. Davies, *J. Chem. Soc., C* 2239 (1966).

²⁴⁸ R. Anet, *Tetrahedron Letters* 3713 (1965).

²⁴⁹ H. Ishihara, *Photochem. Photobiol.* **2**, 455 (1963).

²⁵⁰ S. Y. Wang, *Nature* **190**, 690 (1961).

²⁵¹ D. Kalab, *Experientia* **22**, 24 (1966).

²⁵² A. Wacker, L. Trager, and D. Weinblum, *Angew. Chem.* **73**, 64 (1961).

²⁵³ A. D. McLaren and D. Shugar, "Photochemistry of Proteins and Nucleic Acids," p. 184. Oxford Univ. Press, London and New York, 1964.

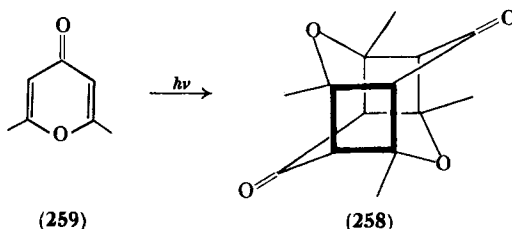
²⁵⁴ R. Beukers, J. Ijlst, and W. Berends, *Rec. Trav. Chim.* **79**, 101 (1960).

²⁵⁵ G. M. Blackburn and R. J. Davies, *J. Am. Chem. Soc.* **89**, 5941 (1967).

between two strands of DNA, but a recent report²⁵⁵ strongly favors the intrastrand mechanism.

In theory, there are four dimeric structures possible on irradiation of thymine, and, in fact, four dimers have been obtained²⁵⁶ from 1,3-dimethylthymine (**253**) by photolysis in aqueous solution; these are the *cis* head-to-head (**254**), the *cis* head-to-tail (**255**), the *trans* head-to-head (**256**), and the *trans* head-to-tail (**257**) dimers, and they appear to be formed via an excited singlet. Irradiation in frozen aqueous solution is reported to yield only the *cis* isomers.²⁵⁷ Four dimers are obtained, however, from the irradiation of frozen aqueous solutions of thymidine²⁵⁸ and 1,3-dimethyluracil²⁵⁹ and from the photosensitized solution dimerization of uracil²⁶⁰ and dimethyluracil.²⁶¹ The photosensitized cyclodimerization of thymine in solution has also been studied.²⁶² The structures of these dimers are not all unambiguously established. The sensitized photochemical cleavage of the thymine dimer has also been discussed.²⁶³

4-Pyranones are reported²⁶⁴ to undergo photochemical dimerization in addition to rearrangement²⁶⁵; exclusive formation of the cage dimer (**258**) from 2,6-dimethylpyran-4-one (**259**) occurs both in the



²⁵⁶ H. Morrison, A. Feeley, and R. Kleopfer, *Chem. Commun.* 358 (1968).

²⁵⁷ D. P. Hollis and S. Y. Wang, *J. Org. Chem.* **32**, 1620 (1967); G. M. Blackburn and R. J. H. Davies, *J. Chem. Soc., C* 1342 (1966).

²⁵⁸ D. Weinblum and H. E. Johns, *Biochim. Biophys. Acta* **114**, 450 (1966).

²⁵⁹ G. Fürst, E. Fahr, and H. Wieser, *Z. Naturforsch.* **22b**, 354 (1967).

²⁶⁰ C. H. Krauch, D. M. Krämer, P. Chandra, P. Mildner, H. Feller, and A. Wacker, *Angew. Chem. Intern. Ed. Engl.* **6**, 956 (1967).

²⁶¹ D. Elad, C. Krüger, and G. M. J. Schmidt, *Photochem. Photobiol.* **6**, 495 (1967).

²⁶² I. von Wilucki, H. Matthäus, and C. H. Krauch, *Photochem. Photobiol.* **6**, 497 (1967).

²⁶³ A. A. Lamola, *J. Am. Chem. Soc.* **88**, 813 (1966).

²⁶⁴ P. Yates and M. J. Jorgenson, *J. Am. Chem. Soc.* **85**, 2956 (1963).

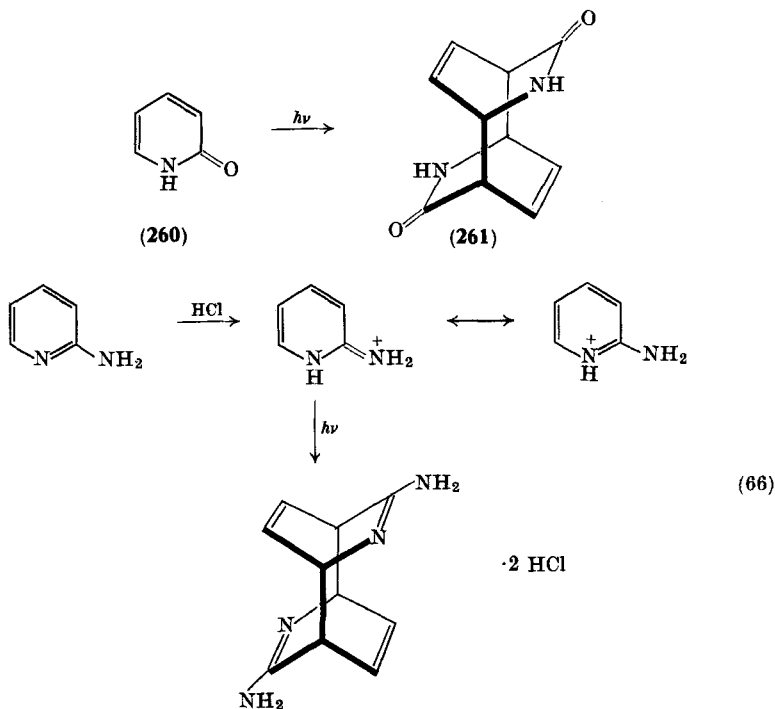
²⁶⁵ P. Yates and I. W. J. Still, *J. Am. Chem. Soc.* **86**, 1208 (1963).

solid state, where it is thought to be the result of crystal packing, and in solution.

2. 1,4-Cycloaddition

2-Pyridone (**260**), unlike quinolin-2-one and coumarin, does not yield a dimer of the cyclobutane type, but on irradiation in concentrated solution is converted into the dimer (**261**) by a novel 1,4-cycloaddition process.^{266, 267} The same dimerization has been observed in a number of nuclear-substituted pyridones.^{266, 268} An analogous process is reported to occur in various 2-aminopyridines [Eq. (66)], on irradiation in acid solution.²⁶⁹

Three dimers are formed²⁶⁹ from the related oxygen heterocycle, 4,6-dimethyl-2-pyranone, by photolysis in benzene; two of these are



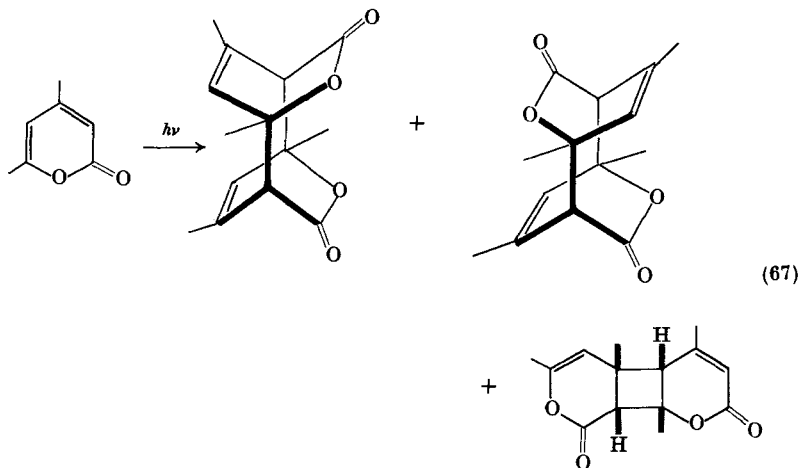
²⁶⁶ W. A. Ayer, R. Hayatsu, P. de Mayo, S. T. Reid, and J. B. Stothers, *Tetrahedron Letters* 648 (1961).

²⁶⁷ E. C. Taylor and R. O. Kan, *J. Am. Chem. Soc.* **85**, 776 (1963).

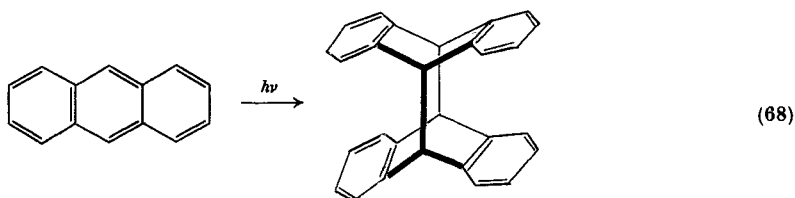
²⁶⁸ L. A. Paquette and G. Slomp, *J. Am. Chem. Soc.* **85**, 765 (1963).

²⁶⁹ P. de Mayo and R. W. Yip, *Proc. Chem. Soc.* **84** (1964).

the result of 1,4-addition, whereas the third is formed by 1,2-addition [Eq. (67)]. Decarboxylation of either β,γ -unsaturated lactone provides a useful route to 1,3,5,7-tetramethyleyclooctatetraene.



Anthracene and certain other polynuclear hydrocarbons have long been known to dimerize readily on photolysis; the formation of such dimers [Eq. (68)] is also the result of 1,4-addition, and is believed to involve a singlet excited state. With substituted anthracenes, the head-to-head dimer is generally formed, although there are exceptions to this rule. Dimerizations probably of a similar nature, have been reported for a number of azaanthracenes including 1-azaanthracene,^{270, 271} 2-azaanthracene,²⁷¹ and benz[*b*]acridine.²⁷² The precise structure of these dimers is uncertain.

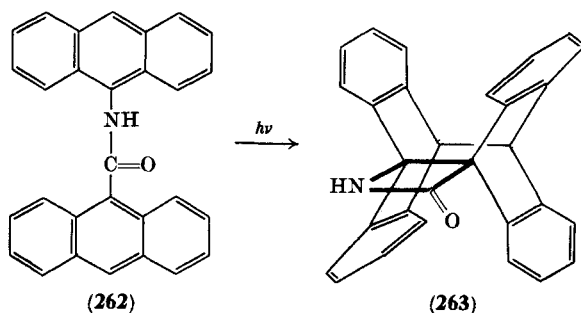


²⁷⁰ A. Étienne, *Ann. Chim. (Paris)* [12] **1**, 5 (1946).

²⁷¹ A. Étienne, *Compt. Rend.* **219**, 622 (1944).

²⁷² A. Étienne and A. Staehelin, *Bull. Soc. Chim. France* 748 (1954).

A series of intramolecular photoadditions of one anthracene nucleus to another resulting in the formation of heterocycles have been reported in certain dianthryl derivatives.²⁷³ 9-Anthryl-9-anthramide (**262**), on irradiation in benzene yields the β -lactam (**263**); the corresponding carbonate and azo compound undergo analogous cyclizations.



V. Synthesis by Photoaddition

This section is concerned with the synthesis of heterocyclic systems by intermolecular addition. The topic can be conveniently divided into a discussion of 1,2- and 1,4-cycloaddition processes.

A. 1,2-CYCLOADDITION

1. The Synthesis of Oxetanes

The synthesis of oxetanes by the photochemical 1,2-cycloaddition of the carbonyl function in aldehydes and ketones to alkenes [Eq. (69)] was first reported by Paterno²⁷⁴ in 1909, and later reinvestigated by Büchi²⁷⁵ in 1954. This reaction has recently been extensively reviewed.^{276, 277} The formation of the oxetane is apparently the result of addition of excited n, π^* triplet carbonyl to an alkene, although for certain aromatic aldehydes and ketones the mechanism is less clear.²⁷⁸

²⁷³ D. E. Applequist, M. A. Lintner, and R. Searle, *J. Org. Chem.* **33**, 254 (1968).

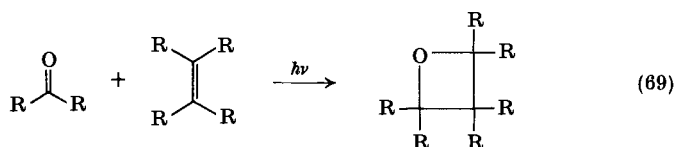
²⁷⁴ E. Paterno and G. Chieffi, *Gazz. Chim. Ital.* **39**, 341 (1909).

²⁷⁵ G. Büchi, C. G. Inman, and E. S. Lipinsky, *J. Am. Chem. Soc.* **76**, 4327 (1954).

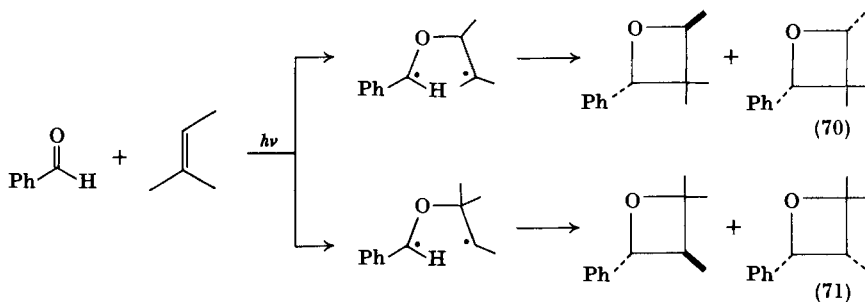
²⁷⁶ D. R. Arnold, *Advan. Photochem.* **6**, 301 (1968).

²⁷⁷ W. L. Dilling, *Chem. Rev.* **66**, 373 (1966).

²⁷⁸ See, for example, N. C. Yang, R. Loeschen, and D. Mitchell, *J. Am. Chem. Soc.* **89**, 5465 (1967); N. C. Yang and R. L. Loeschen, *Tetrahedron Letters* 2571 (1968).



When the reaction is applied to an unsymmetrically substituted alkene, the major photoproduct or products are those arising from the most stable diradical intermediate. This is illustrated in the irradiation of benzaldehyde in 2-methylbut-2-ene in which the principal products are the stereoisomeric oxetanes arising from the same diradical intermediate [Eq. (70)].²⁷⁸ The oxetanes resulting from addition in the alternative sense [Eq. (71)] are minor products, as are other products arising by allylic hydrogen abstraction.



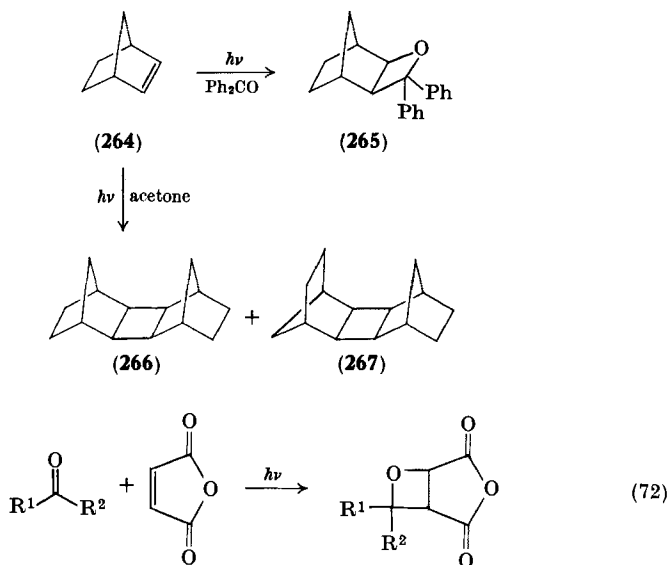
The addition of aliphatic aldehydes and ketones to alkenes is less successful as a preparative procedure for oxetanes. An essential requirement for addition is that the triplet energy of the alkene must be considerably greater than that of the carbonyl. If this condition is not fulfilled, energy transfer to the alkene can occur,²⁷⁹ sensitizing, for example, dimerization of the alkene. This is clearly illustrated^{280, 281} for norbornene (**264**) which on irradiation in the presence of benzophenone (E_T 68.5 kcal/mole) forms the adduct **265**; photolysis in acetone (E_T 75 kcal/mole) affords only norbornene dimers (**266** and **267**), whereas acetophenone, which has intermediate triplet energy (E_T 73.6 kcal/mole) forms both oxetanes and norbornene dimers.

²⁷⁹ D. R. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Letters* 1425 (1964).

²⁸⁰ D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Am. Chem. Soc.* **87**, 2596 (1965).

²⁸¹ D. Scharf and K. Forte, *Tetrahedron Letters* 821 (1963).

The photocycloaddition of aliphatic ketones to the electron-deficient double bonds of *trans*-1,2-dicyanoethylene^{282, 283} and maleic anhydride²⁸² [Eq. (72)] is believed to proceed by an alternative mechanism involving nucleophilic attack on the double bond by the n, π^* singlet state of the carbonyl.



The Paterno-Büchi reaction has been employed in the synthesis, often in high yield, of a large variety of substituted oxetanes. In addition to simple aliphatic and aromatic alkenes, cycloaddition of ketones to, for example, fumaronitrile,²⁸⁴ 1,3-diacetylimidazolin-2-one²⁸⁵ [Eq. (73)], and allenes²⁸⁶ has been reported. Allenes yield both 1,5- and 1,6-dioxaspiro[3.3]heptanes as well as the 2-alkylidene-oxetane; this is illustrated for benzophenone and tetramethylallene in Eq. (74). Cycloaddition of ketones to ketenimines to form 2- and

²⁸² N. J. Turro, P. Wriede, J. C. Dalton, D. Arnold, and A. Glick, *J. Am. Chem. Soc.* **89**, 3950 (1967).

²⁸³ N. J. Turro, P. A. Wriede, and J. C. Dalton, *J. Am. Chem. Soc.* **90**, 3274 (1968).

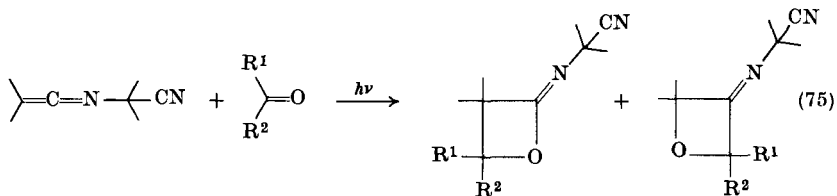
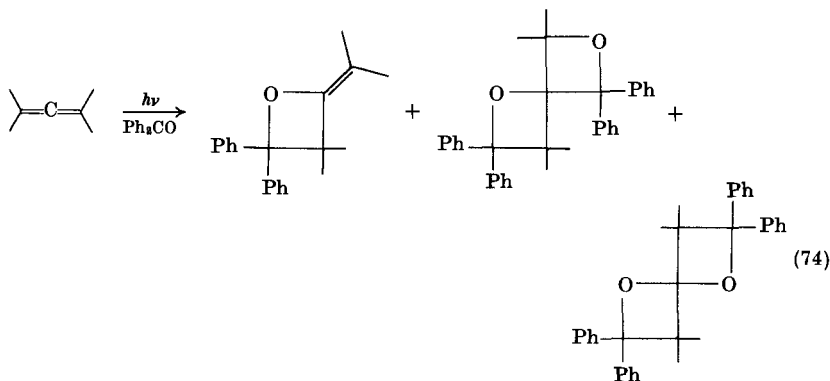
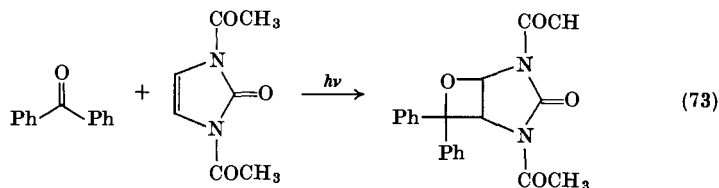
²⁸⁴ J. J. Beereboom and M. S. von Wittenau, *J. Org. Chem.* **30**, 1231 (1965).

²⁸⁵ G. Steffan and G. O. Schenck, *Chem. Ber.* **100**, 3961 (1967).

²⁸⁶ H. Gotthardt, R. Steinmetz, and G. S. Hammond, *Chem. Commun.* 480 (1967); *J. Org. Chem.* **33**, 2774 (1968).

3-iminooxetanes has also been observed²⁸⁷ [Eq. (75)], and the mechanism discussed.²⁸⁸

A further cycloaddition of interest is that of aldehydes and ketones to furans.²⁸⁹ The oxetane and dioxetanes formed from furan and benzophenone have been the subject of considerable study, and are now believed²⁹⁰ to have the detailed structure and stereochemistry



shown in Eq. (76). Substituted furans also undergo this photo-addition,²⁹¹ but other five-membered heterocycles such as thiophene, pyrrole, and isoxazole do not react in this way.²⁹⁰

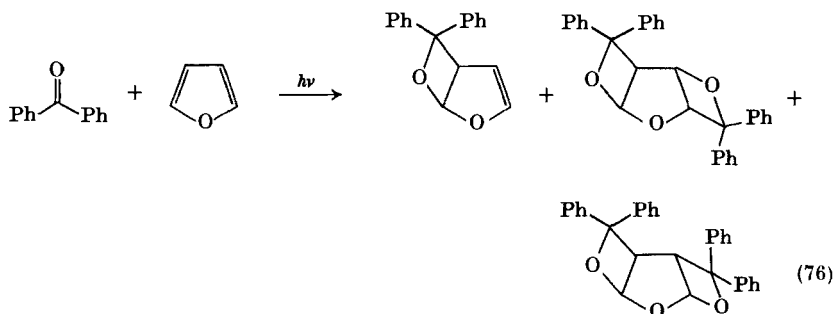
²⁸⁷ L. A. Singer and P. D. Bartlett, *Tetrahedron Letters* 1887 (1964).

²⁸⁸ L. A. Singer and G. A. Davis, *J. Am. Chem. Soc.* **89**, 598 (1967).

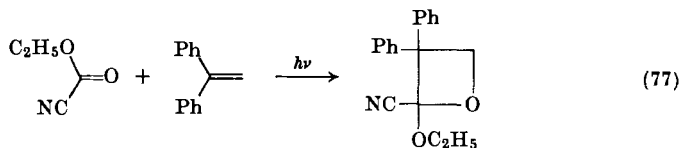
²⁸⁹ K. Shima and H. Sakurai, *Bull. Chem. Soc. Japan* **39**, 1806 (1966).

²⁹⁰ G. R. Evanega and E. B. Whipple, *Tetrahedron Letters* 2163 (1967).

²⁹¹ C. Rivas and E. Payo, *J. Org. Chem.* **32**, 2918 (1967).



Considerable variation is also possible in the carbonyl function, and in addition to simple aldehydes and ketones, acetyl cyanide,²⁹² diethyl oxomalonate,²⁹³ diethyl oxalate,²⁹⁴ and ethyl cyanofornate²⁹⁵ [Eq. (77)] will all undergo cycloaddition to alkenes to form the corresponding oxetanes. Oxetanes are also formed in certain circumstances from both α,β -unsaturated aldehydes²⁹⁶ and acetylenic ketones.²⁹⁷



There are a few reports in the literature in which the carbonyl group has been formally replaced by another unsaturated function. Thiobenzophenone (**268**) undergoes photochemical 1,2-cycloaddition to α -phellandrene (**269**) to give the thietane (**270**), together with the sulfur heterocycles (**271** and **272**) formed by 1,4-cycloaddition.²⁹⁸ Isoprene, cyclopentadiene, and 1,4-diphenylbutadiene also undergo 1,4-cycloaddition with thiobenzophenone, but 1,3-cyclooctadiene

²⁹² Y. Shigemitsu, Y. Odaira, and S. Tsutsumi, *Tetrahedron Letters* 55 (1967).

²⁹³ M. Hara, Y. Odaira, and S. Tsutsumi, *Tetrahedron Letters* 2981 (1967).

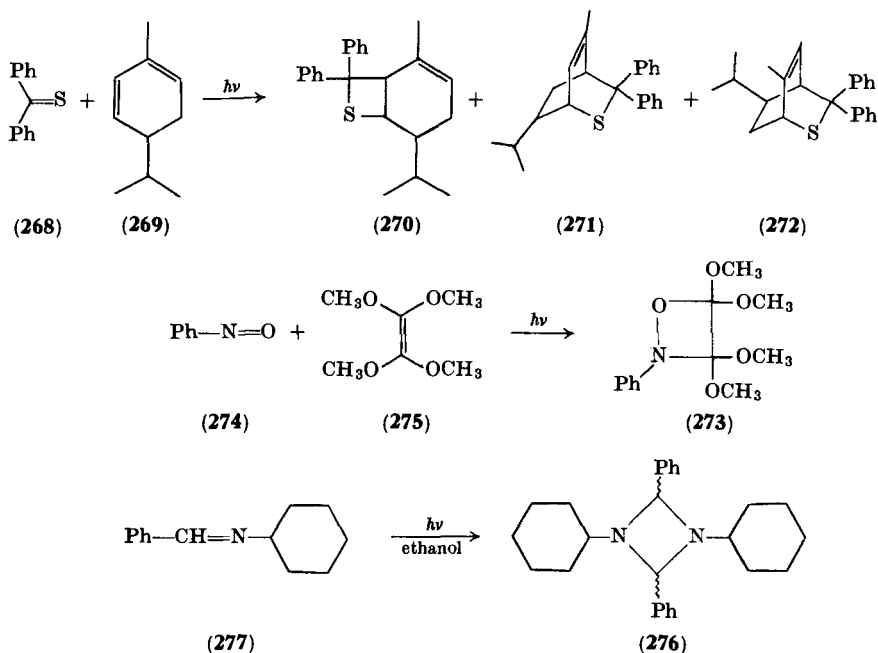
²⁹⁴ T. Tominaga, Y. Odaira, and S. Tsutsumi, *Bull. Chem. Soc. Japan* **40**, 2451 (1967).

²⁹⁵ Y. Odaira, T. Shimodaira, and S. Tsutsumi, *Chem. Commun.* 757 (1967).

²⁹⁶ R. A. Schneider and J. Meinwald, *J. Am. Chem. Soc.* **89**, 2023 (1967).

²⁹⁷ G. T. Kwiatkowski and D. B. Selley, *Tetrahedron Letters* 3471 (1968).

²⁹⁸ Y. Omote, M. Yoshioka, K. Yamada, and N. Sugiyama, *J. Org. Chem.* **32**, 3676 (1967).



yields only the 1,2-adduct.²⁹⁹ The oxazetidine (273) is formed³⁰⁰ by the photoaddition of nitrosobenzene (274) to tetramethoxyethylene (275), and *N,N'*-dicyclohexyl-2,4-diphenyl-1,3-diazetidine (276) is obtained³⁰¹ by photochemical dimerization of the imine (277) in ethanol. The conversion of *N-p*-dimethylaminobenzylideneaniline into *trans*-azobenzene and *cis*-4,4'-bis(dimethylamino)stilbene by photolysis in ether is thought to involve an intermediate 1,2-diazetidine.³⁰²

The intramolecular equivalent of the Paterno-Büchi reaction has been observed in a number of unsaturated ketones. A series of γ,δ -unsaturated ketones (278) are converted in this way into the oxabicyclo[2.2.0]hexanes (279) and the oxabicyclo[2.1.1]hexanes (280), both photoproducts being the result of 1,2-cycloaddition.³⁰³

²⁹⁹ K. Yamada, M. Yoshioka, and N. Sugiyama, *J. Org. Chem.* **33**, 1240 (1968).

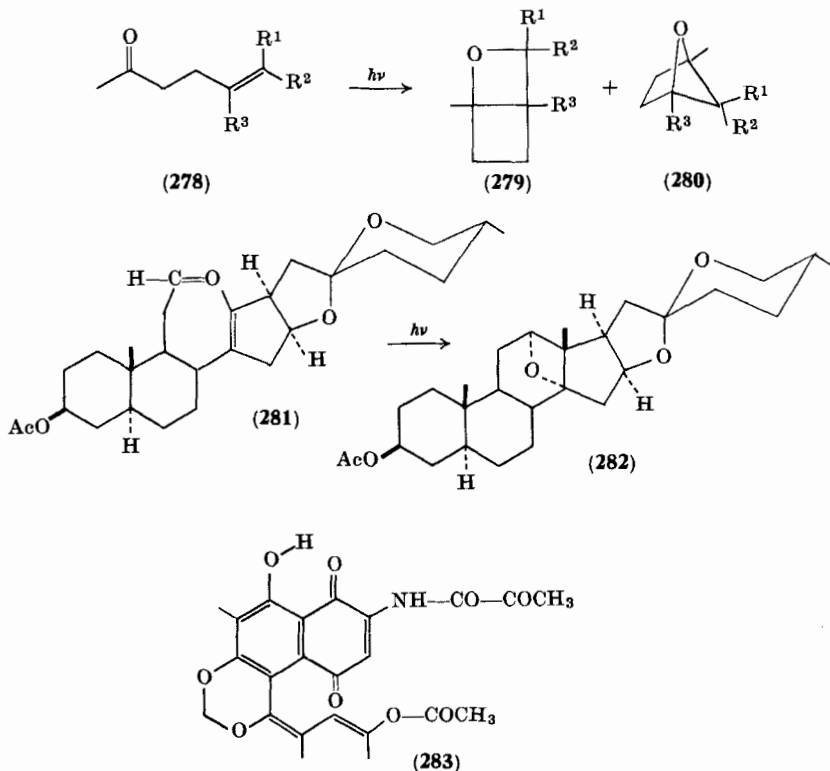
³⁰⁰ R. W. Hoffmann and H. Hauser, *Angew. Chem. Intern. Ed. Engl.* **3**, 380 (1964).

³⁰¹ R. O. Kan and R. L. Furey, *J. Am. Chem. Soc.* **90**, 1666 (1968).

³⁰² S. Searles and R. A. Clasen, *Tetrahedron Letters* 1627 (1965).

³⁰³ N. C. Yang, M. Nussim, and D. R. Coulson, *Tetrahedron Letters* 1525 (1965).

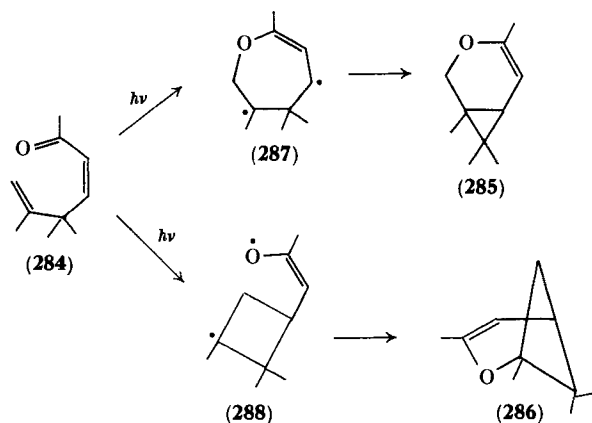
An analogous addition is observed in the conversion of lumihecogenin acetate (**281**) into photohecogenin acetate (**282**),³⁰⁴ and an addition of this type has also been proposed to account for the photolytic loss of acetic anhydride in streptovaricin (**283**).³⁰⁵



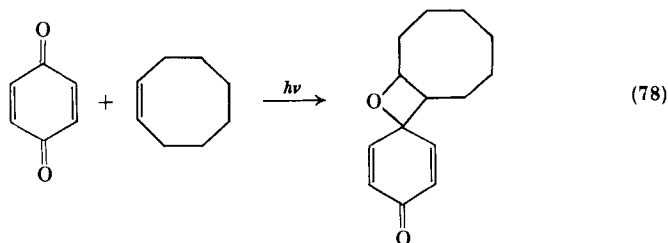
Intramolecular photoaddition in *cis*-5,5,6-trimethylhepta-3,6-dien-2-one (**284**) takes a different course,²⁹⁶ yielding not the oxetane but the two dihydropyrans (**285** and **286**). This is in contrast to the intermolecular cycloaddition of α,β -unsaturated aldehydes to alkenes which affords only oxetanes, and has been accounted for in terms of diradical intermediates (**287** and **288**) formed from the *s-cis* conformation (**284**) of the dienone. The intermolecular equivalent is thought to occur by addition to the *s-trans* conformation.

³⁰⁴ P. Bladon, W. McMeekin, and I. A. Williams, *J. Chem. Soc.* 5727 (1963).

³⁰⁵ R. J. Schacht and K. L. Rinehart, *J. Am. Chem. Soc.* **89**, 2239 (1967).



Photoaddition of alkenes to *p*-quinones has also been observed; cyclooctene, for example, undergoes addition to *p*-benzoquinone³⁰⁶ [Eq. (78)] and anthraquinone³⁰⁷ to form oxetanes. Furthermore,



oxetanes (289 and 290) result from the dimerization of 2,5- and 2,6-dimethylbenzoquinone,³⁰⁸ although the more usual mode of addition leads to the formation of cyclobutane derivatives. *p*-Benzoquinone, on the other hand, undergoes 1,4-cycloaddition to butadiene and 2,3-dimethylbutadiene to give the dihydropyran rather than an oxetane [Eq. (79)].³⁰⁹ The equivalent cycloaddition is not observed with anthraquinone,³⁰⁷ and this is attributed to the higher triplet energy of anthraquinone ($E_T = 62.5$ kcal/mole; *p*-benzoquinone

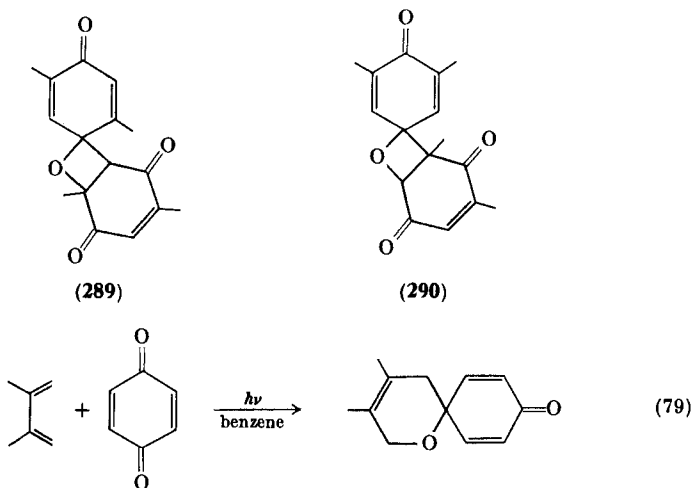
³⁰⁶ D. Bryce-Smith, A. Gilbert, and M. G. Johnson, *J. Chem. Soc. C* 383 (1967).

³⁰⁷ D. Bryce-Smith, A. Gilbert, and M. G. Johnson, *Tetrahedron Letters* 2863 (1968).

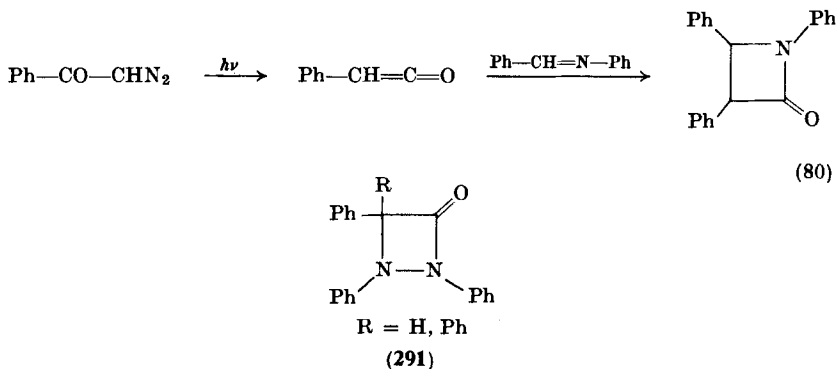
³⁰⁸ R. C. Cookson, J. J. Frankel, and J. Hudec, *Chem. Commun.* 16 (1965).

³⁰⁹ J. A. Barltrop and B. Hesp, *J. Chem. Soc.* 5182 (1965).

$E_T = 50$ kcal/mole) which permits it to be quenched by butadiene ($E_T = 60$ kcal/mole).



Other 1,2-cycloadditions have been accomplished photochemically. The photolytic decomposition of diazoketones in the presence of imines to give azetidinones [see, for example, Eq. (80)] is sometimes preferable³¹⁰ to the direct chemical addition of ketene to imine. Diazetidinones of general structure (291) can be prepared³¹¹ either by thermal or photochemical addition of ketenes to azobenzenes, or by photolysis of diazoketones in azobenzene.

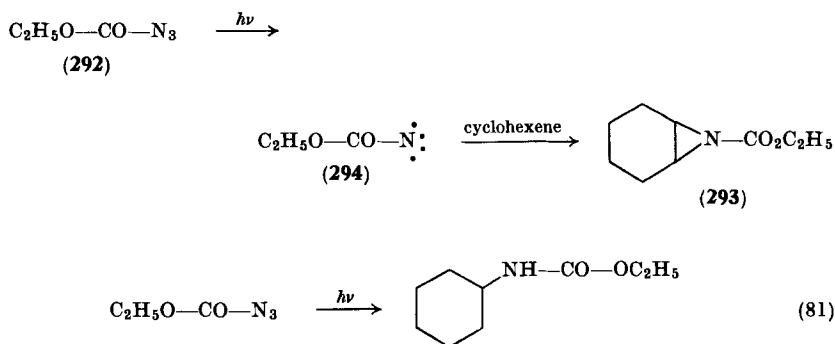


³¹⁰ W. Kirmse and L. Horner, *Chem. Ber.* **89**, 2759 (1956).

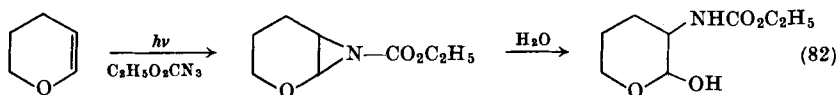
³¹¹ L. Horner and E. Spietschka, *Chem. Ber.* **89**, 2765 (1956).

2. The Photolysis of Ethyl Azidoformate

The photolysis of ethyl azidoformate (**292**) in cyclohexene gives rise to a good yield of 7-carbethoxy-7-azabicyclo[4.1.0]heptane (**293**),³¹² and a similar formation of aziridines has been observed in other simple alkenes and dienes.³¹³ This reaction is believed to take place via formation of a nitrene (**294**), followed by a 1,2-cycloaddition of this nitrene to the carbon-carbon double bond; an identical product mixture is obtained³¹⁴ when the nitrene is generated from *N-p*-nitrobenzenesulfonyloxyurethan. Photoproducts arising by insertion reactions of the nitrene into C-H bonds are also observed, and this mode of reaction occurs almost exclusively when ethyl azidoformate is photolyzed in cyclohexane to give cyclohexylurethan [Eq. (81)].³¹² Insertion is also reported on photolysis in dioxane.³¹⁵



Aziridines are formed in this way from certain enol acetates³¹⁶ and from dihydropyran³¹⁷ [Eq. (82)], but these are relatively unstable,



³¹² W. Lwowski and T. W. Mattingly, *J. Am. Chem. Soc.* **87**, 1947 (1965).

³¹³ A. Mishra, S. N. Rice, and W. Lwowski, *J. Org. Chem.* **33**, 481 (1968).

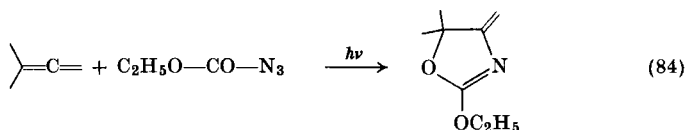
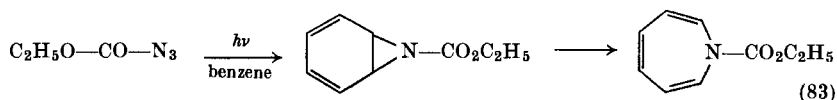
³¹⁴ W. Lwowski and T. J. Maricich, *J. Am. Chem. Soc.* **87**, 3630 (1965).

³¹⁵ H. Nozaki, S. Fujita, H. Takaya, and R. Noyori, *Tetrahedron* **23**, 45 (1967).

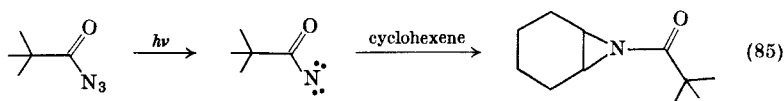
³¹⁶ J. F. W. Keana, S. B. Keana, and D. Beetham, *J. Org. Chem.* **32**, 3057 (1967).

³¹⁷ I. Brown and O. E. Edwards, *Can. J. Chem.* **43**, 1266 (1965).

and with water are immediately converted into the corresponding hydroxyurethan. When the photodecomposition of ethyl azidoformate is carried out in benzene³¹⁸ *N*-carbethoxyazepine is obtained, presumably via the intermediate aziridine [Eq. (83)]. This reaction was later extended to substituted benzenes.³¹⁹ The photoaddition of ethyl azidoformate to 1,1-dimethylallene to give 2-ethoxy-5,5-dimethyl-4-methylene-2-oxazoline [Eq. (84)] has recently been reported.³²⁰



The photolysis of acyl azides has also been studied, and in some respects these appear to behave analogously. Pivaloyl azide, for example, adds to cyclohexene to give a 26% yield of an aziridine [Eq. (85)],³²¹ and the assumption is that this addition again occurs via a nitrene. The photodecomposition of acetyl azide (295) in benzonitrile and phenylacetylene, on the other hand, affords³²² 2-methyl-5-phenyl-1,3,4-oxadiazole (296) and 2-methyl-5-phenyloxazole (297),



respectively, and must be the result of a 1,3-cycloaddition to the intermediate (298).

Photolysis of 2,3-diphenylcycloprop-2-ene-1-acetic acid azide (299) yields 2,5-diphenylpyrrole (300), 3,4-diphenyl-2-pyridone (301), and 5,6-diphenyl-2-pyridone (302), and these are interpreted as

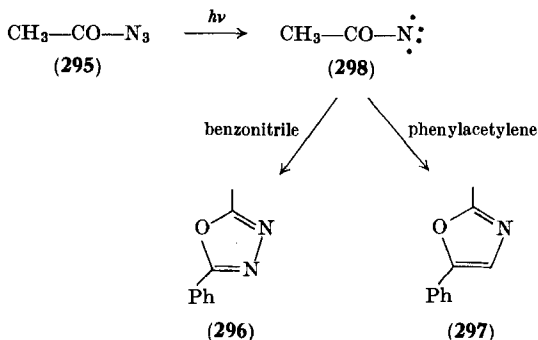
³¹⁸ W. Lwowski, T. J. Maricich, and T. W. Mattingly, *J. Am. Chem. Soc.* **85**, 1200 (1963).

³¹⁹ K. Hafner, D. Zinser, and K. L. Moritz, *Tetrahedron Letters* 1733 (1964).

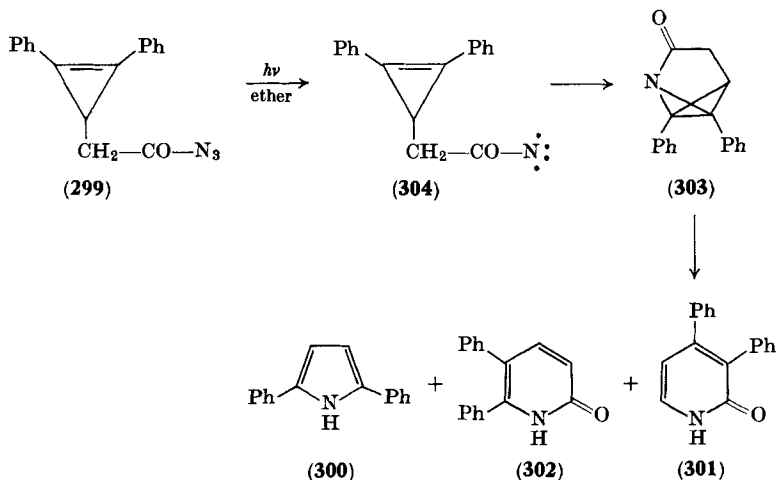
³²⁰ R. F. Bleiholder and H. Shechter, *J. Am. Chem. Soc.* **90**, 2131 (1968).

³²¹ W. Lwowski and G. T. Tissue, *J. Am. Chem. Soc.* **87**, 4022 (1965).

³²² R. Huisgen and J. P. Anselme, *Chem. Ber.* **98**, 2998 (1965).



arising from the tricyclic species (303), formed by intramolecular addition of the nitrene (304).³²³



B. 1,4-CYCLOADDITION

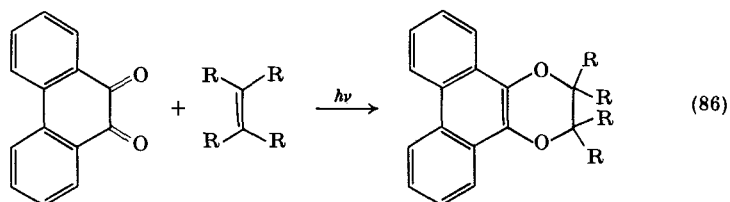
1. The Formation of 1,4-Dioxenes

The photoinduced 1,4-cycloaddition of alkenes to phenanthraquinone to give substituted 1,4-dioxenes [Eq. (86)] in good yield was first observed in 1944.³²⁴ The addition has since then been more fully investigated, and is applicable to a variety of *o*-quinones and aromatic

³²³ N. C. Castellucci, M. Kato, H. Zenda, and S. Masamune, *Chem. Commun.* 473 (1967).

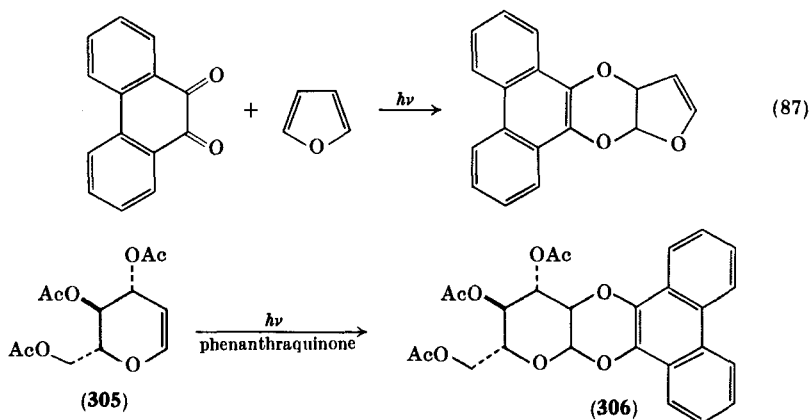
³²⁴ A. Schönberg and A. Mustafa, *J. Chem. Soc.* 387 (1944).

α -diketones and to both conjugated and nonconjugated olefins. A comprehensive review of the literature has recently been published.³²⁵



Excellent yields of adduct have been obtained from a variety of *o*-quinones, including *o*-benzoquinone, 1,2-naphthaquinone, phenanthraquinone, 5,6-chrysenequinone, and many of their simple derivatives, including the heterocyclic quinone³²⁶ benzo[*h*]quinoline-5,6-quinone. Lower yields are in general observed for aromatic diketones such as benzil,³²⁷ and the reaction does not appear to occur to any appreciable extent with aliphatic α -diketones.

A large number of nonconjugated and conjugated alkenes have been successfully employed in this addition,³²⁵ and examples of

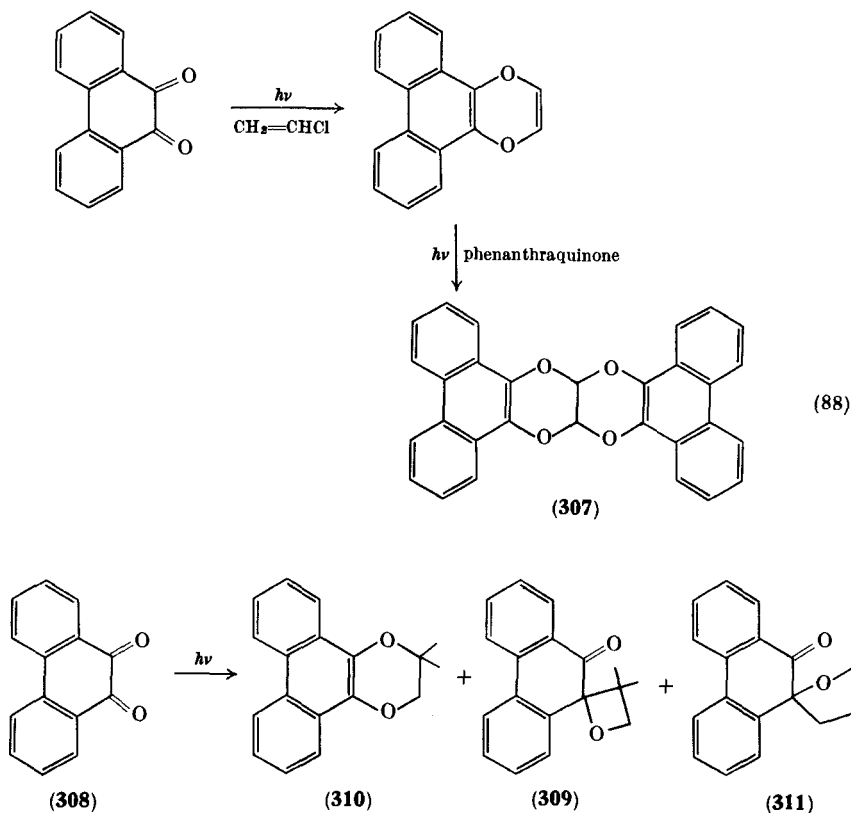


³²⁵ G. Pfundt and G. O. Schenck, in "1,4-Cycloaddition Reactions" (J. Hamer, ed.), p. 347. Academic Press, New York, 1967.

³²⁶ A. Mustafa, A. K. Mansour, and A. F. A. M. Shalaby, *J. Am. Chem. Soc.* **81**, 3409 (1959).

³²⁷ A. Schönberg and A. Mustafa, *J. Chem. Soc.* 551 (1945).

analogous additions to diphenylketene³²⁸ and alkoxyacetylenes³²⁵ have also been reported. Of particular interest in the present context are the additions which occur to the oxygen heterocycles—furan³²⁹ [Eq. (87)], dihydrofuran,³²⁹ 1,4-dioxene,³³⁰ and certain benzopyrans.^{329, 331} Certain unsaturated sugar derivatives react³³² similarly with phenanthraquinone, for example, 3,4,6-triacetyl-D-glucal (305), which gives the adduct (306).



³²⁸ A. Schönberg and A. Mustafa, *J. Chem. Soc.* 997 (1947).

³²⁹ C. H. Krauch, S. Farid, and G. O. Schenck, *Chem. Ber.* **98**, 3102 (1965).

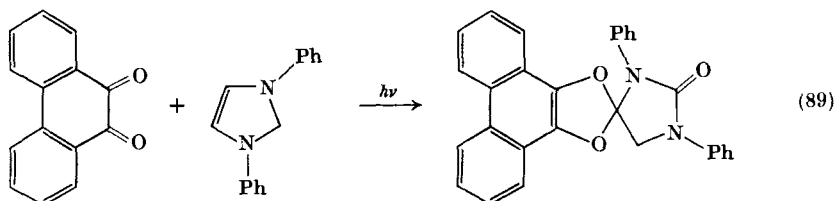
³³⁰ W. M. Horspool and G. D. Khandelwal, *Chem. Commun.* 1203 (1967).

³³¹ A. Schönberg, N. Latif, R. Moubasher, and W. I. Awad, *J. Chem. Soc.* 374 (1950).

³³² B. Helferich and M. Gindy, *Chem. Ber.* **87**, 1488 (1954), and references cited therein.

Addition of vinyl chlorides is often accompanied by the elimination of HCl; this is observed in the addition of chlorostilbene to phenanthraquinone,³²⁷ and accounts for the formation of the adduct (307) from phenanthraquinone and vinyl chloride [Eq. (88)].³³³

The study of this cycloaddition and its mechanism is complicated by the formation in small yield of additional photoproducts. Irradiation of phenanthraquinone (308) in, for example, 2-methylpropene affords the oxetane (309), arising by 1,2-cycloaddition of the alkene to the carbonyl, in addition to the expected 1,4-dioxene (310).³³⁴ Oxetanes are the principal products of photoaddition of phenanthraquinone to benzofuran, furano[3,2-*g*]coumarin, and isocoumarin.³²⁹ A further product has the structure (311), and is undoubtedly the



result of initial hydrogen abstraction by the excited quinone from the alkene, followed by addition of the resulting allyl radical. A recent communication reports the additional formation of a phenanthrodioxole in 10% yield from phenanthraquinone and 1,2-di-*t*-butylethylene, chlorostilbene, or *N,N*-diphenylimidazolinone [Eq. (89)].³³⁵ The mechanism of the formation of this dioxole is not clear, although preliminary investigations suggest that it may arise from the corresponding ketooxetane.

The stereochemistry of this addition has been the subject of recent investigations. The photoaddition of either *cis*- or *trans*-stilbene to phenanthraquinone (312) results in the formation of both *cis*- (313) and *trans*-1,4-cycloadducts (314), and similar observations have been made with 1-phenylpropene.³³⁶ There is, however, a partial stereospecificity in this process which is reduced with increasing tempera-

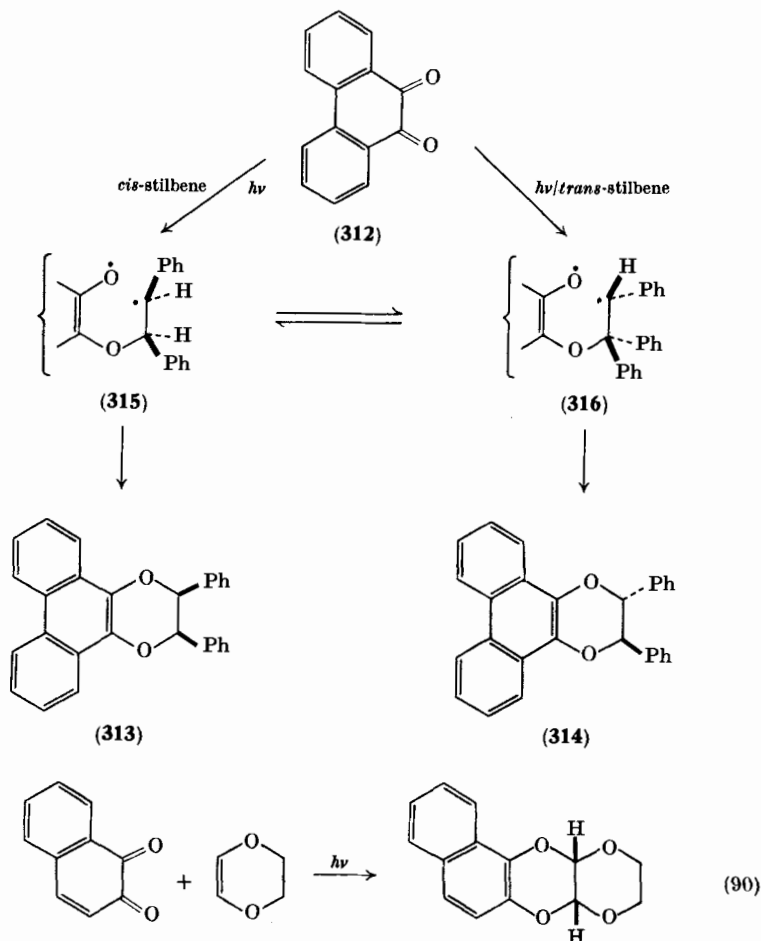
³³³ G. Pfundt and G. O. Schenck, in "1,4-Cycloaddition Reactions" (J. Hamer, ed.), p. 359. Academic Press, New York, 1967.

³³⁴ S. Farid and K.-H. Scholz, *Chem. Commun.* 412 (1968).

³³⁵ S. Farid, D. Hess, G. Pfundt, K.-H. Scholz, and G. Steffan, *Chem. Commun.* 638 (1968).

³³⁶ S. Farid, *Chem. Commun.* 1268 (1967).

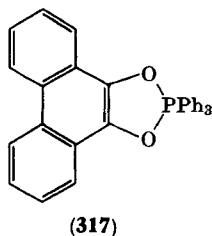
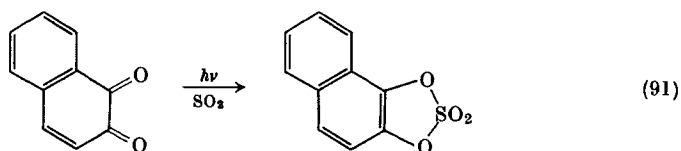
ture. These observations can be rationalized on the basis of the assumption that attack by the excited triplet quinone on the alkenes gives rise to two intermediate diradicals (**315** and **316**) and that in these species there is competition between free rotation and cyclization to the corresponding 1,4-dioxene. The addition of either *cis*- or *trans*-but-2-ene to phenanthraquinone gives, on the other hand, an identical mixture of *cis* and *trans* adducts,³³⁷ while the addition of 1,2-naphthaquinone to *p*-dioxenes is said to give only the *cis* isomer [Eq. (90)].³³⁰



³³⁷ Y. L. Chow and T. C. Joseph, *Chem. Commun.* 604 (1968).

2. Miscellaneous 1,4-Cycloadditions

A number of other photochemical 1,4-cycloadditions leading to the formation of heterocyclic systems have been reported, but in general these are less well investigated. The irradiation of *o*-quinones in the presence of sulfur dioxide affords, often in good yield, the corresponding 1,3,2-dioxathiole or cyclic sulfate³³⁸ [see, for example, Eq. (91)]. Reaction of phenanthraquinone with triphenylphosphine can be achieved photochemically³³⁹ or thermally and the product is thought to have the cyclic structure (317).



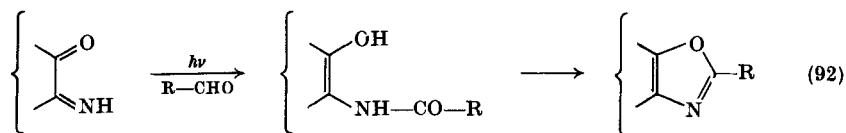
The photochemical addition of both aliphatic and aromatic aldehydes to *o*-quinones monoimines has been widely used in the preparation of oxazoles [Eq. (92)].³⁴⁰ An intermediate amide has been isolated in a number of cases, and can be thermally converted into the oxazole. The reaction, therefore, does not appear to be a cycloaddition. An analogous addition occurs between *o*-quinones and aldehydes, and the photoproducts have been shown to have an acyclic structure³⁴¹ rather than the previously assigned 1,3-dioxole structure.

³³⁸ G. O. Schenck and G. A. Schmidt-Thomé, *Ann. Chem.* **584**, 199 (1953).

³³⁹ G. Pfundt and G. O. Schenck, in "1,4-Cycloaddition Reactions" (J. Hamer, ed.), p. 379. Academic Press, New York, 1967.

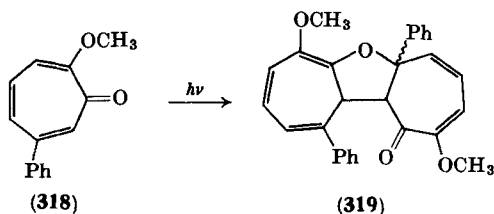
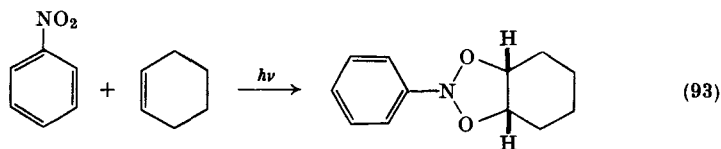
³⁴⁰ G. Pfundt and G. O. Schenck, in "1,4-Cycloaddition Reactions" (J. Hamer, ed.), p. 402. Academic Press, New York, 1967.

³⁴¹ J. M. Bruce, *Quart. Rev. (London)* **21**, 405 (1967).



C. MISCELLANEOUS ADDITIONS

The photoaddition of nitrobenzene to cyclohexene at -70° results in the formation of the first reported 1,3,2-dioxazole [Eq. (93)].³⁴² A novel dimerization is observed in the photolysis of 2-methoxy-6-phenyltropone (318) to the furan derivative (319) in low yield.³⁴³ This is regarded as the first 1,8-dipolar photoaddition to be observed.



VI. Synthesis by Photocyclization

A. OXIDATIVE PHOTOCYCLIZATION; HETEROCYCLIC ANALOGS OF PHENANTHRENE

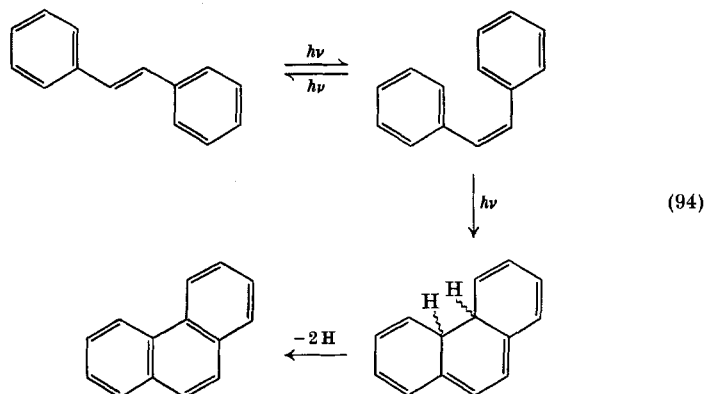
The photocyclization of stilbene and its simple derivatives to phenanthrene and substituted phenanthrenes is now a well-documented and useful synthetic reaction; the scope and mechanism of this reaction have been thoroughly reviewed by Stermitz.³⁴⁴ There

³⁴² J. L. Charlton and P. de Mayo, *Can. J. Chem.* **46**, 1041 (1968).

³⁴³ T. Mukai, T. Miyashi, and M. C. Woods, *Tetrahedron Letters* 433 (1967).

³⁴⁴ F. R. Stermitz, in "Organic Photochemistry" (O. L. Chapman, ed.), Vol. 1, p. 247. Dekker, New York, 1967.

is considerable evidence for the intermediacy of the dihydrophenanthrene [Eq. (94)], formed directly from the excited *cis*-stilbene, although there is still some doubt concerning the stereochemistry of this species. *Cis-trans* photoisomerism occurs readily in stilbene as does photodimerization in more concentrated solution, and phenanthrenes are therefore obtained from either isomer. The dehydrogenation of dihydrophenanthrene to phenanthrene is the result of hydrogen abstraction by oxygen to other acceptors such as iodine, and



the reaction is commonly carried out in the presence of about 5% dissolved iodine. Cyclodehydrogenation is also achieved in a number of cases by irradiation of the appropriate 2-iodostilbene.³⁴⁵

Increasingly, this process has been adapted to the synthesis of heterocyclic systems. One or both of the phenyl substituents in stilbene can be replaced by a heteroaromatic system, and some of the more important of these cyclizations are recorded in Table I. The formation of benz[*h*]isoquinoline by photolysis of 4-styrylpyridine in cyclohexane is accompanied by the formation of 1- and 3-cyclohexylbenz[*h*]isoquinoline.³⁴⁶

The photocyclization of stilbenes to phenanthrenes has been used in the synthesis of the aporphine ring system^{347, 348}; conversion of the

³⁴⁵ S. M. Kupchan and H. C. Wormser, *J. Org. Chem.* **30**, 3792 (1965).

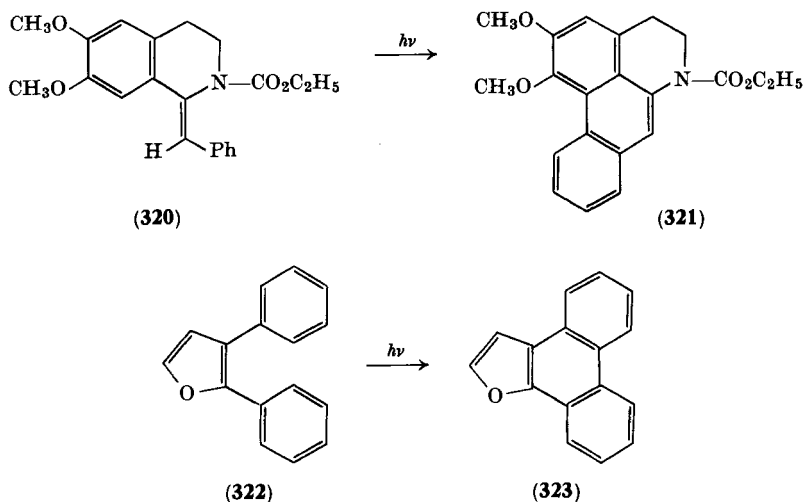
³⁴⁶ C. E. Loader and C. J. Timmons, *J. Chem. Soc., C* 1457 (1967).

³⁴⁷ M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Letters* 2937 (1966).

³⁴⁸ N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Letters* 2941 (1966); *J. Am. Chem. Soc.* **88**, 5368 (1966).

tetrahydroisoquinoline (**320**) into *N*-carbethoxy-6 α ,7-dehydronor-nuciferine (**321**) by photolysis in ethanol in the presence of iodine is the vital step in a new synthesis of *dl*-nuciferine.³⁴⁷

A cyclization has also been reported in which the carbon-carbon double bond of styrene forms part of a heterocyclic system; in this, 2,3-diphenylfuran (**322**) is converted by irradiation in benzene into phenanthra[9,10-*b*]furan (**323**).³⁴⁹



It has been known for some time that irradiation of azobenzene (**324**) in either 22 *N* sulfuric acid^{350, 351} or acetic acid with added ferric chloride³⁵² yields benzo[*c*]cinnoline (**325**). This is accompanied by the formation of an almost equal quantity of benzidine (**326**), undoubtedly arising by rearrangement of hydrazobenzene (**327**). The mechanism of this reaction differs, therefore, from that of the stilbene cyclo-dehydrogenation, and azobenzene itself functions as the hydrogen acceptor. Yields of not more than 50% of benzo[*c*]cinnoline are generally observed.

³⁴⁹ A. Padwa and R. Hartman, *J. Am. Chem. Soc.* **88**, 3759 (1966).

³⁵⁰ G. E. Lewis, *J. Org. Chem.* **25**, 2193 (1960).

³⁵¹ G. M. Badger, R. J. Drewer, and G. E. Lewis, *Australian J. Chem.* **16**, 1042 (1963).

³⁵² P. Hugelshofer, J. Kalvoda, and K. Schaffner, *Helv. Chim. Acta* **43**, 1322 (1960).

TABLE I

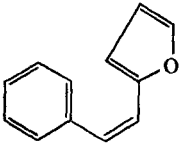
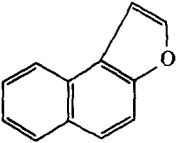
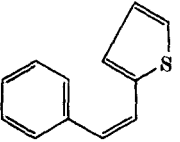
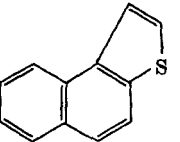
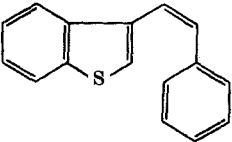
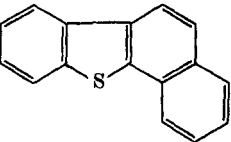
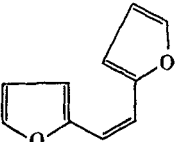
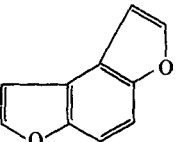
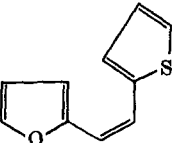
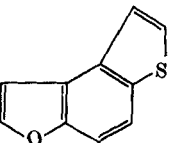
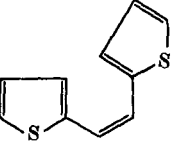
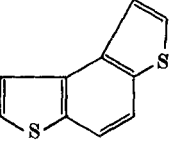
<i>cis</i> -Stilbene analog	Photoproducts	Ref.
		<i>a</i>
 <p>and derivatives</p>		<i>b</i> <i>c</i>
 <p>and derivatives</p>		<i>b, c</i>
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		<i>a, d</i>
 <p>and derivatives</p>		<i>a, d</i>

TABLE I—continued

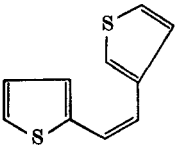
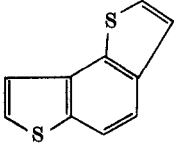
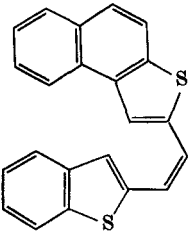
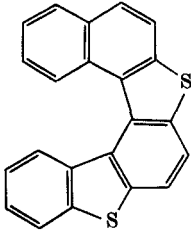
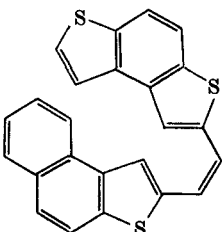
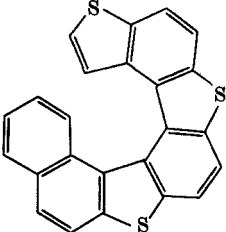
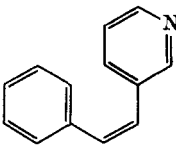
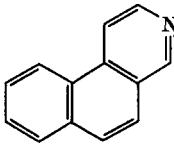
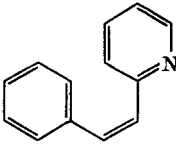
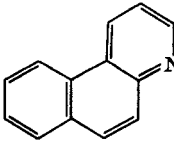
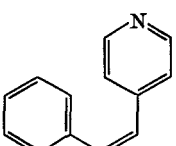
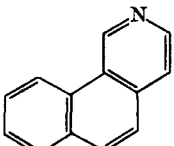
<i>cis</i> -Stilbene analog	Photoproducts	Ref.
		<i>d</i>
		<i>e</i>
		<i>e</i>
		<i>f, g</i>
		<i>f, g</i>
		<i>f, g</i>

TABLE I—continued

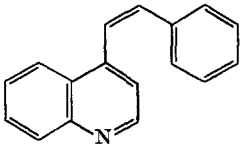
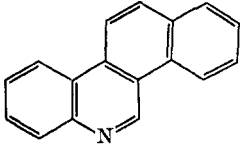
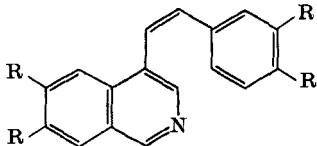
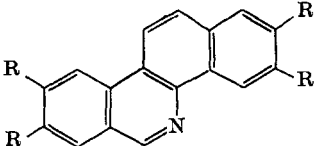
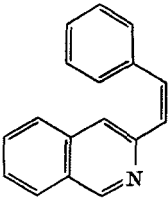
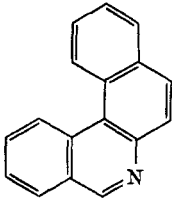
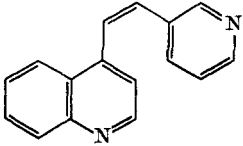
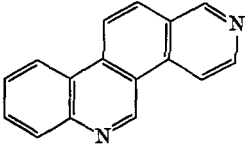
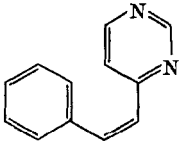
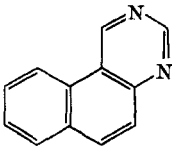
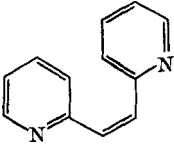
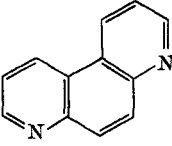
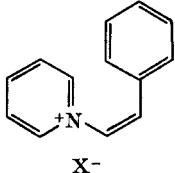
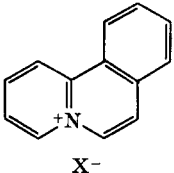
<i>cis</i> -Stilbene analog	Photoproducts	Ref.
		<i>h</i>
 <p>R = H R = OCH₃</p>		<i>h</i> <i>i</i>
		<i>h</i>
		<i>h</i>
		<i>j</i>
		<i>k</i>

TABLE I.—*continued*

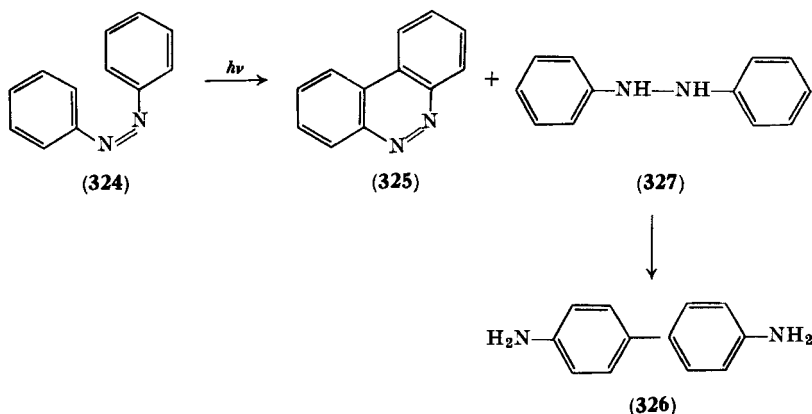
<i>cis</i> -Stilbene analog	Photoproducts	Ref.
	+	<i>k</i>
		<i>k</i>
	+ +	<i>k</i>
	+	<i>k</i>
		<i>k</i>

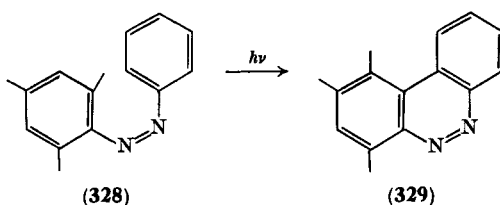
TABLE I—continued

<i>cis</i> -Stilbene analog	Photoproducts	Ref.
		1

^a C. E. Loader and C. J. Timmons, *J. Chem. Soc.*, C 1677 (1967).^b W. Carruthers and H. N. M. Stewart, *Tetrahedron Letters* 301 (1965).^c W. Carruthers and H. N. M. Stewart, *J. Chem. Soc.* 6221 (1965).^d R. M. Kellog, M. B. Groen, and H. Wynberg, *J. Org. Chem.* **32**, 3093 (1967).^e H. Wynberg and M. B. Groen, *J. Am. Chem. Soc.* **90**, 5339 (1968).^f C. E. Loader and C. J. Timmons, *J. Chem. Soc.* 1078 (1966).^g P. Bartolus, G. Cauzzo, and L. G. Galiazzo, *Tetrahedron Letters* 239 (1966).^h C. E. Loader and C. J. Timmons, *J. Chem. Soc.*, C 330 (1968).ⁱ S. F. Dyke and M. Sainsbury, *Tetrahedron* **23**, 3161 (1967).^j C. E. Loader and C. J. Timmons, *J. Chem. Soc.*, C 1343 (1967).^k H.-H. Perkampus and G. Kassebeer, *Ann. Chem.* **696**, 1 (1966).^l R. E. Doolittle and C. K. Bradsher, *J. Org. Chem.* **31**, 2616 (1966).

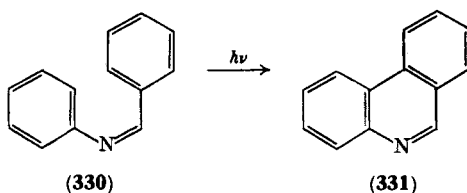
This cyclization has also been observed in a variety of substituted azobenzenes,³⁴⁴ and is sometimes accompanied by the expulsion of methyl, chloro, iodo, and carbethoxy substituents from the position of cyclization. In the photocyclization of 2,4,6-trimethylazobenzene (328), a methyl migration is observed leading to the formation of





1,2,4-trimethylbenzo[c]cinnoline (329).³⁵³ Recent work on the photolysis of bisazo compounds has been reported.³⁵⁴

Certain aromatic imines undergo a similar cyclodehydrogenation to the phenanthridine. Benzylideneaniline (330) yields phenanthridine (331) only in sulfuric acid,³⁵⁵ whereas diphenylmethylenedianiline cyclizes in the presence of oxygen or iodine.³⁵⁶ Cyclizations have also been reported in Schiff's bases formed from α - and β -naphthylamine³⁵⁷ and from 4-aminoquinoline,³⁵⁸ and in the mesomeric betaine 4,5-diphenyl-2-mercapto-1,3,4-thiadiazolium hydroxide.³⁵⁹ Irradiation of the anil of 2-aminonaphthalene (332) in ethanol, however, leads to incorporation of ethanol and the formation of 3-phenylbenzo[f]-quinoline (333).³⁶⁰ Additional photoproducts are obtained when the photolysis is carried out in *n*-hexanol.³⁶¹



³⁵³ G. M. Badger, R. J. Drewer, and G. E. Lewis, *Australian J. Chem.* **19**, 643 (1966).

³⁵⁴ N. C. Jamieson and G. E. Lewis, *Australian J. Chem.* **20**, 321, 2777 (1967).

³⁵⁵ G. M. Badger, C. P. Joshua, and G. E. Lewis, *Tetrahedron Letters* 3711 (1964).

³⁵⁶ F. B. Mallory and C. S. Wood, *Tetrahedron Letters* 2643 (1965).

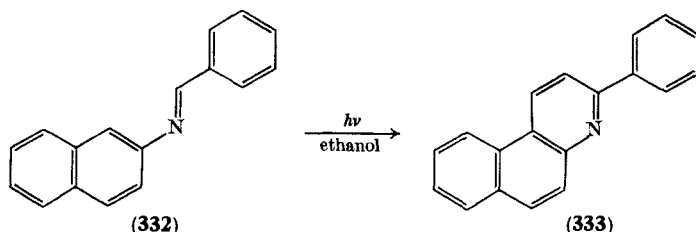
³⁵⁷ M. P. Cava and R. H. Schlessinger, *Tetrahedron Letters* 2109 (1964).

³⁵⁸ V. M. Clark and A. Cox, *Tetrahedron* **22**, 3421 (1966).

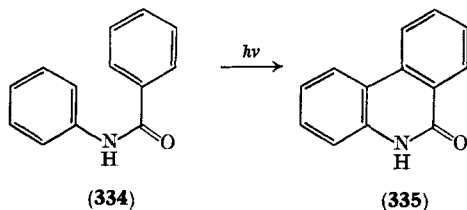
³⁵⁹ R. M. Moriarty, J. M. Kliegman, and R. B. Desai, *Chem. Commun.* 1255 (1967).

³⁶⁰ J. S. Shannon, H. Silberman, and S. Sternhell, *Tetrahedron Letters* 659 (1964).

³⁶¹ P. J. Collin, H. Silberman, S. Sternhell, and G. Sugowdz, *Tetrahedron Letters* 2063 (1965).



A number of related reactions are worthy of mention. Benzanilide (334) is converted into phenanthridone (335) by irradiation in benzene in the presence of iodine.³⁶² Cyclodehydrogenation is also observed in the anilides of indole-2-carboxylic acid and indole-3-carboxylic acid on irradiation in acetone.³⁶³ Irradiation of diphenylamine³⁶⁴ and certain of its *N*-substituted derivatives³⁶⁵ yields the corresponding carbazole. The mechanism of this reaction differs from



that of the stilbene cyclodehydrogenation in that molecular hydrogen is evolved and that the reaction appears to be inhibited by oxygen; α -, β -, γ -, and δ -carbolines have been synthesized in this way from the appropriate anilinopyridine.³⁶⁶

The first synthesis of the unstable pyrido[2,1-*a*]isoindole system has been achieved by a cyclization of this type; *N*-benzyl-2-bromopyridinium salts (336) on irradiation yield the pyrido[2,1-*a*]iso-

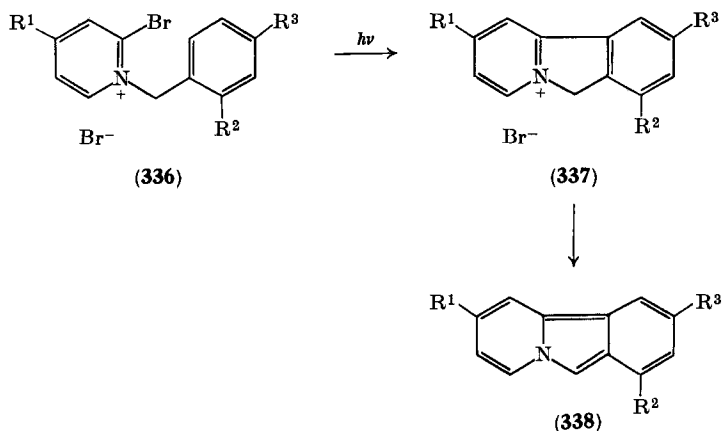
³⁶² B. S. Thyagarajan, N. Kharasch, H. B. Lewis, and W. Wolf, *Chem. Commun.* 614 (1967).

³⁶³ E. Winterfeldt and H. J. Altmann, *Angew. Chem. Intern. Ed. Engl.* **7**, 466 (1968).

³⁶⁴ E. J. Bowen and J. H. D. Eland, *Proc. Chem. Soc.* 202 (1963).

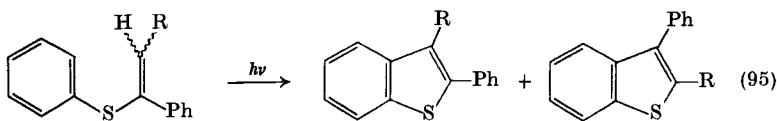
³⁶⁵ K. H. Grellmann, G. M. Sherman, and H. Linschitz, *J. Am. Chem. Soc.* **85**, 1881 (1963).

³⁶⁶ V. M. Clark, A. Cox, and E. J. Herbert, *J. Chem. Soc., C* 831 (1968).



indolium salts (337), and these can be converted into the parent pyrido[2,1-a]isoindole (338) by treatment with carbonate.³⁶⁷

Finally, the photocyclization of certain phenylthioethylenes to give benzo[*b*]thiophene derivatives [see, for example, Eq. (95)] has been reported.³⁶⁸



B. CYCLIZATION OF HALOGEN-CONTAINING COMPOUNDS

1. The Hofmann-Loeffler Reaction

The cyclization of *N*-halogenated amines to pyrrolidines, the Hofmann-Loeffler reaction,³⁶⁹ can be effected by irradiation in sulfuric acid, followed by treatment with base. The initial step in the conversion³⁷⁰ of *N*-chlorodibutylamine to 1-butylpyrrolidine [Eq. (96)] is photochemically induced homolytic cleavage of the nitrogen-

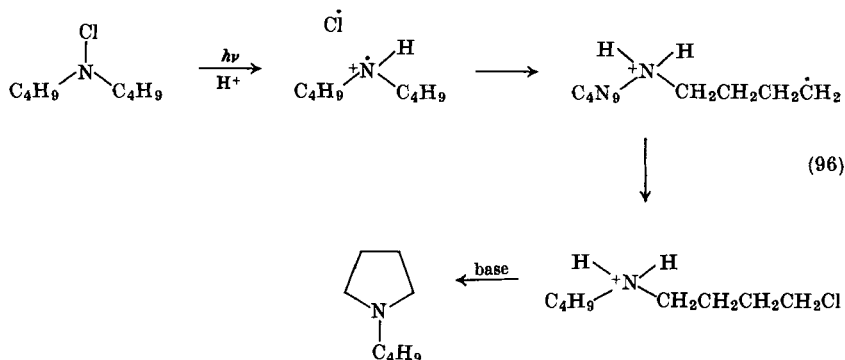
³⁶⁷ A. Fozard and C. K. Bradsher, *J. Org. Chem.* **32**, 2966 (1967).

³⁶⁸ S. H. Groen, R. M. Kellogg, J. Buter, and H. Wynberg, *J. Org. Chem.* **33**, 2218 (1968).

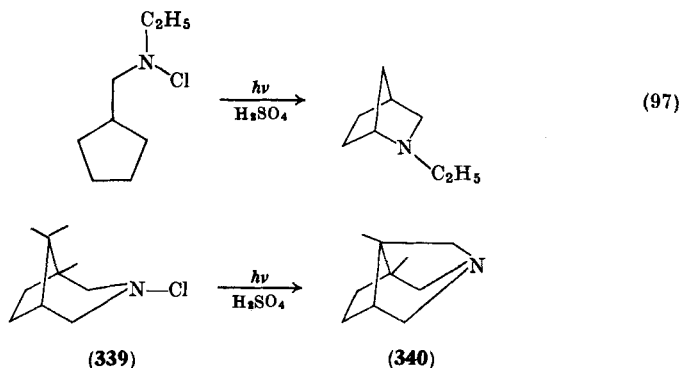
³⁶⁹ M. E. Wolff, *Chem. Rev.* **63**, 55 (1963).

³⁷⁰ S. Wawzonek and T. P. Culbertson, *J. Am. Chem. Soc.* **81**, 3367 (1959).

chlorine bond in the protonated species; this is followed by intramolecular hydrogen abstraction from the δ -carbon atom and recombination of the radical thus formed with chlorine to give the



chloroamine. Cyclization is then achieved by base. This reaction has been successfully employed in the synthesis of quinuclidines,^{371, 372} 2-azabicyclo[2.2.1]heptanes³⁷³ [see, for example, Eq. (97)], octahydroindolizines,³⁷⁴ and pyrrolizidines,³⁷⁵ and in the same way, irradiation of *N*-chlorocamphidine (339) yields the tricyclic amine (340).³⁷⁶ The Hofmann–Loeffler reaction is also an important step



³⁷¹ R. Lukeš and M. Ferles, *Chem. Listy* **49**, 510 (1955).

³⁷² S. Wawzonek, M. F. Nelson, and P. J. Thelson, *J. Am. Chem. Soc.* **73**, 2806 (1951).

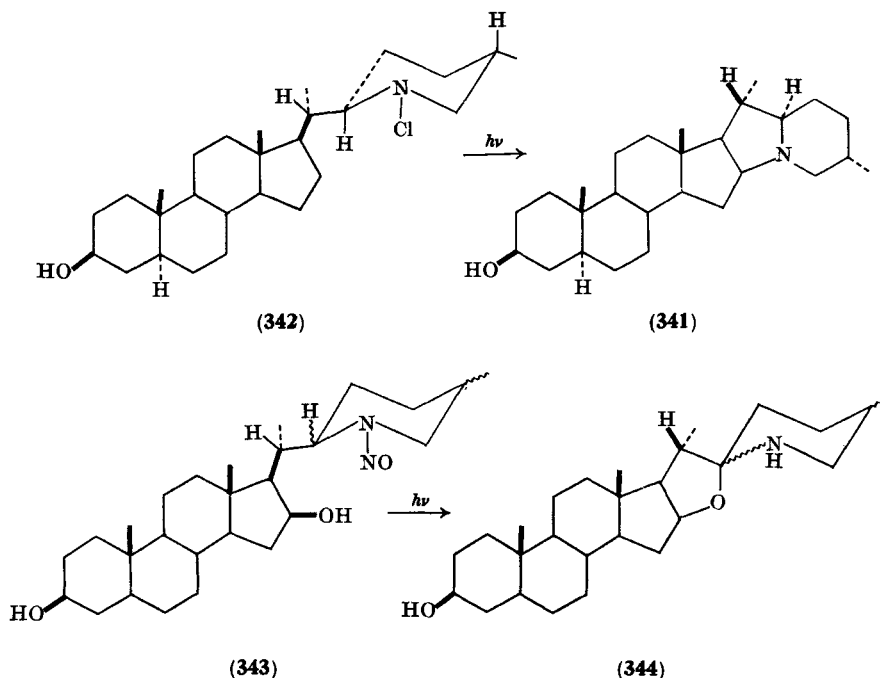
³⁷³ P. G. Gassman and D. C. Herbert, *Tetrahedron* **21**, 2725 (1965).

³⁷⁴ M. F. Grundon and B. E. Reynolds, *J. Chem. Soc.* 3898 (1963).

³⁷⁵ E. Schmitz and D. Murawski, *Chem. Ber.* **93**, 754 (1960).

³⁷⁶ W. R. Hertler and E. J. Corey, *J. Org. Chem.* **24**, 572 (1959).

in the synthesis of certain of the *Solanum* alkaloids. Demissidine (**341**) has been obtained in this fashion from the *N*-chloro derivative (**342**)³⁷⁷; the epimeric *N*-chloro amine, (2*S*:25*R*)-*N*-chloro-22,26-imino-5 α -



cholestan-3 β -ol, does not undergo cyclization on irradiation in trifluoroacetic acid, but rather is degraded to the stereoisomeric 20-chloropregnane, as are both the corresponding 16 β -hydroxy derivatives.³⁷⁸ Photolysis of the stereoisomeric *N*-nitroso-22,26-iminocholestan-3 β ,16 β -diols (**343**) in acid solution, however, results in the formation³⁷⁹ of the spirosolane alkaloids soladulcidine, solasodine, and tomatidine (**344**).

N-Chloroimides undergo an analogous photoreaction to give γ -chloroimides, and this has been used in a new synthesis of substituted γ -lactones.³⁸⁰

³⁷⁷ G. Adam and K. Schreiber, *Tetrahedron* **20**, 1719 (1964).

³⁷⁸ G. Adam and K. Schreiber, *Tetrahedron* **22**, 3581 (1966).

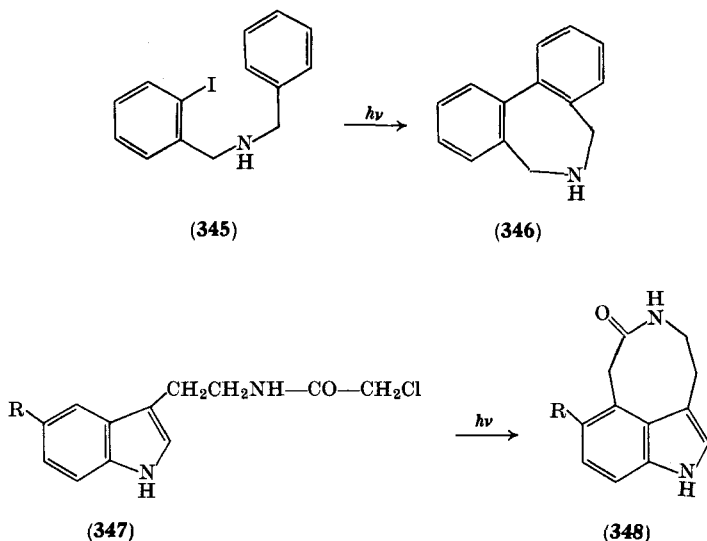
³⁷⁹ G. Adam and K. Schreiber, *Tetrahedron* **22**, 3591 (1966).

³⁸⁰ R. C. Petterson and A. Wambsgans, *J. Am. Chem. Soc.* **86**, 1648 (1964).

2. Miscellaneous Halogen-Containing Compounds

The photolysis of aryl iodides is of use in the preparation of bi-phenyls, and the application of this reaction to the synthesis of phenanthrenes has already been discussed. Seven- and 8-membered nitrogen-containing heterocycles can also be obtained by an intramolecular arylation of this type; photolysis of the iodoamine (345) affords, for example, 6,7-dihydro-5*H*-dibenz[*c,e*]azepine (346).³⁸¹

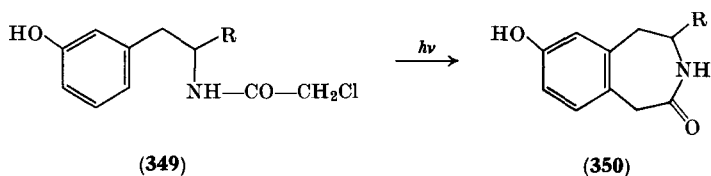
Photocyclizations have also been observed in certain *N*-chloroacetyl derivatives. *N*-(Chloroacetyl)tryptamine (347; R = H), its 5-methoxy derivative (347; R = OCH₃), and the corresponding tryptophans give good yields of the tricyclic derivatives (348) on irradiation in neutral aqueous solution.³⁸² Similarly, *N*-chloroacetyl-*m*-tyramine (349; R = H) and *N*-chloroacetyl-*m*-tyrosine (349; R = CO₂H), undergo cyclization to the tetrahydrobenzazepinones (350) in 70% yield³⁸³; cyclizations are also observed in the catecholamines and in certain mescaline derivatives.³⁸³



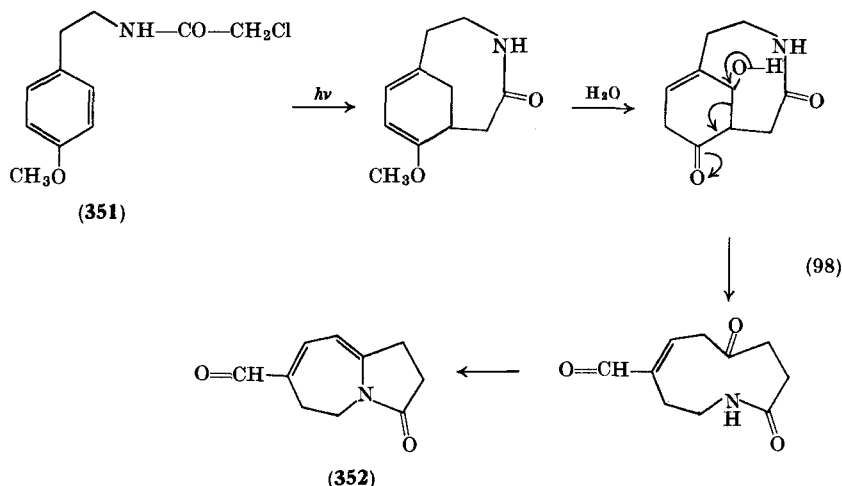
³⁸¹ P. W. Jeffs and J. F. Hansen, *J. Am. Chem. Soc.* **89**, 2798 (1967).

³⁸² O. Yonemitsu, B. Witkop, and I. L. Karle, *J. Am. Chem. Soc.* **89**, 1039 (1967).

³⁸³ O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Am. Chem. Soc.* **90**, 776 (1968).



N-Chloroacetyl-*p*-*O*-methyltyramine (351) behaves in a different fashion and, on irradiation, is converted into the bicyclic rearrangement product (352).^{382, 383} The suggestion has been made that this rearrangement is the result of homolytic carbon-chlorine bond cleavage, followed by radical attack on the aromatic system, and the proposed sequence of events is outlined in Eq. (98).

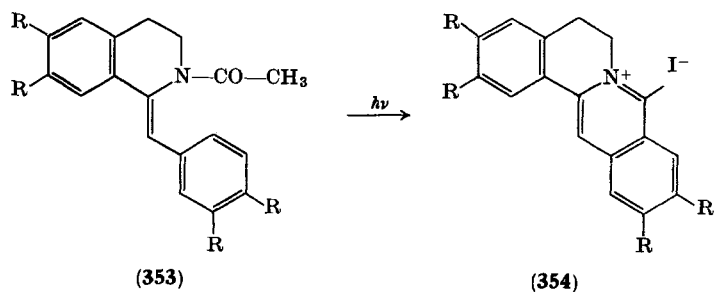


C. MISCELLANEOUS PHOTOCYCLIZATIONS

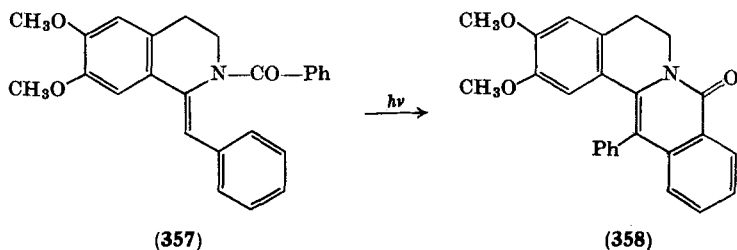
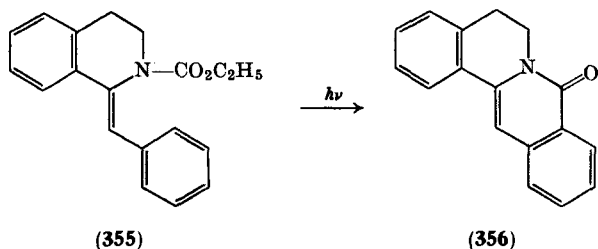
1. Nitrogen Heterocycles

Irradiation of 2-acetyl-1-benzylidene-1,2,3,4-tetrahydroisoquinoline (353; R = H) in methanol in the presence of iodine results in the formation in good yield of 8-methylprotoberberinium iodide (354; R = H)³⁸⁴ and not of the dehydroaporphane system which might be expected by analogy with oxidative cyclization of *cis*-stilbene

³⁸⁴ G. R. Lenz and N. C. Yang, *Chem. Commun.* 1136 (1967).



derivatives. The tetramethoxy derivative (**353**; $R = \text{OCH}_3$) similarly yields the photoproduct (**354**; $R = \text{OCH}_3$), and this can be converted into β -coralydine by reduction with sodium borohydride. The corresponding 2-carbethoxy derivative (**355**) similarly undergoes photochemically induced intramolecular acylation to give oxyprotoberberine (**356**), as well as oxidative cyclization to the dehydroaporphine system.³⁸⁵ *Trans*-1-benzylidene-2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**357**), on the other hand, behaves quite

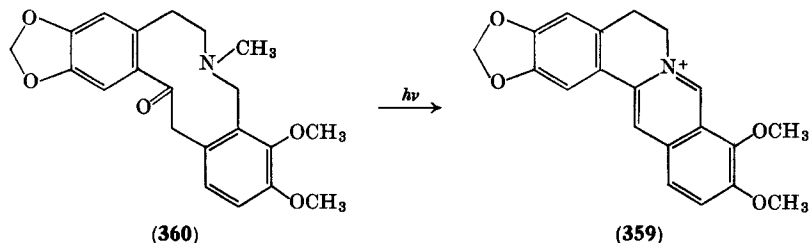


differently, and on irradiation in ethanol in the presence of iodine undergoes a novel oxidative cyclization to form the tetracyclic product (**358**).³⁸⁶

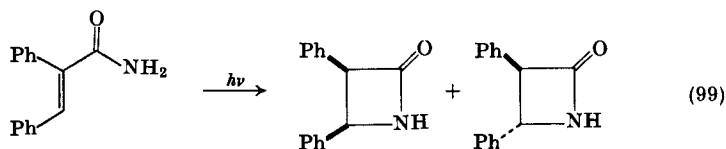
³⁸⁵ N. C. Yang, A. Shaní, and G. R. Lenz, *J. Am. Chem. Soc.* **88**, 5369 (1966).

³⁸⁶ M. P. Cava and S. C. Havlicek, *Tetrahedron Letters* 2625 (1967).

Certain berberine alkaloids can also be directly prepared from the appropriately substituted protopine alkaloid by photolysis in ethanol.³⁸⁷ Berberine itself (359) is obtained in this way from α -alocryptopine (360), and similar preparations of epiberberine and coptisine have been recorded.



The cyclization of α,β -unsaturated amides to lactams has recently been reported by Chapman.³⁸⁸ Irradiation of *cis*- α -phenylcinnamide in benzene in the absence of oxygen leads to the formation of *cis*- and *trans*-3,4-diphenylazetidin-2-one [Eq. (99)] in low yield, with the former predominating. α,β -Unsaturated acids are similarly converted into the corresponding β -lactones.

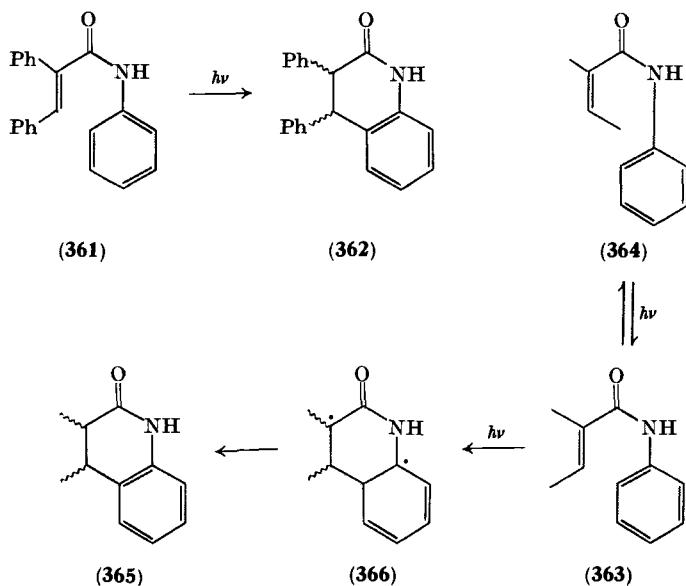


Azetidinones are also formed on photolysis of *cis*- α -phenylcinnamanilide (361), but in addition a small quantity of a *cis-trans* mixture of 3,4-diphenyl-3,4-dihydroquinolin-2-one (362) was obtained. The yield of quinolinone was considerably increased in the photocyclization of alkyl-substituted acrylanilides.³⁸⁹ The anilide (363) of tiglic acid, for example, was converted into the anilide (364) of angelic acid by photochemical *cis-trans* isomerism, and into a mixture of *cis*- and *trans*-3,4-dimethyl-3,4-dihydroquinolin-2-one (365) in 58% yield by irradiation in ether. In this cyclization and in

³⁸⁷ X. A. Dominguez and J. G. Delgado, *Tetrahedron Letters* 2493 (1967).

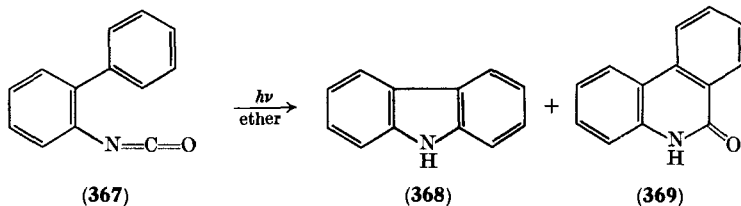
³⁸⁸ O. L. Chapman and W. R. Adams, *J. Am. Chem. Soc.* **90**, 2333 (1968).

³⁸⁹ P. G. Cleveland and O. L. Chapman, *Chem. Commun.* 1064 (1967).



other similar cyclizations of *trans*-crotonanilide and α -methylacrylanilide, no β -lactam formation was observed. The diradical species (366), or its dipolar equivalent, is probably an intermediate in this process, and is further converted into the quinolinone by a 1,3-hydrogen shift.

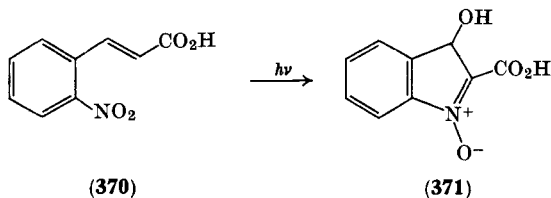
Nonoxidative photocyclization also occurs in 2-diphenyl isocyanate (367) to form carbazole (368) and phenanthridone (369).³⁹⁰ The mechanism of this transformation is uncertain, and, in fact, little attention has been given to the photochemistry of isocyanates. Carbazole is also the principal product of nonsensitized photolysis of 2-azidobiphenyl³⁹¹; the reaction presumably involves the cyclization of an intermediate nitrene.



³⁹⁰ J. S. Swenton, *Tetrahedron Letters* 2855 (1967).

³⁹¹ J. S. Swenton, *Tetrahedron Letters* 3421 (1968).

A number of interesting photocyclizations have been reported in aromatic nitro compounds. The first authenticated example is probably that of Tănăsescu³⁹² who showed that photolysis of 2-nitrocinnamic acid (**370**) led to the formation of 3-hydroxy-3*H*-indole-2-carboxylic acid 1-oxide (**371**). Although the mechanism of



this transformation is not completely clear, it is undoubtedly related to that postulated³⁹³ [Eq. (100)] for the well-known conversion of *o*-nitrobenzaldehyde into *o*-nitrosobenzoic acid. Intramolecular hydrogen abstraction followed by oxygen transfer can also be used to account for the photolytic transformation of certain *o*-nitrophenyl-dihydropyridines to the correspondingly substituted *o*-nitrosophenyl-pyridines [Eq. (101)].³⁹⁴ The synthesis of 2-phenylisatogen (**372**) from the salt (**373**)³⁹⁵ and by irradiation of 2-nitrotolan (**374**) in pyridine^{396, 397} may be related mechanistically. A series of substituted 2-phenylisatogens (**375**; $\text{R} = \text{NMe}_2$, OH or OCH_3) has also been prepared³⁹⁸ by irradiation of the appropriate *o*-nitrostilbene (**376**); the isatogens are probably derived from the analogous nitroso intermediates (**377**) by cyclization and oxidation.

The major products of photolysis at pH 8 of a series of *N*-substituted 2,4-dinitrophenylamino acids of general formula **378** are 4-nitro-2-nitrosoaniline (**379**), the aldehyde (**380**), and carbon dioxide^{399, 400}; the formation of the nitroso function may well be

³⁹² I. Tănăsescu, *Bull. Soc. Chim. France* **41**, 1074 (1927).

³⁹³ P. de Mayo and S. T. Reid, *Quart. Rev. (London)*, **15**, 414 (1961).

³⁹⁴ J. A. Berson and E. Brown, *J. Am. Chem. Soc.* **77**, 447 (1955).

³⁹⁵ F. Kröhnke and I. Vogt, *Chem. Ber.* **85**, 376 (1952).

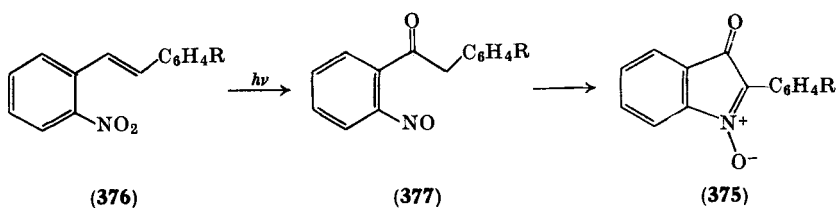
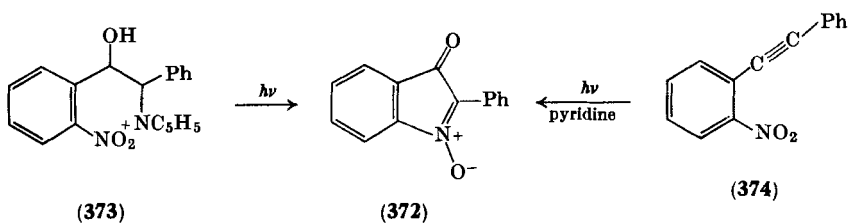
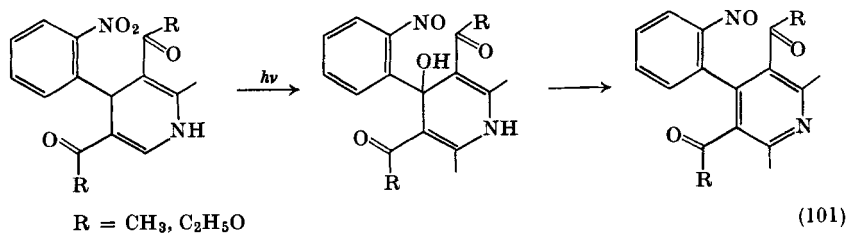
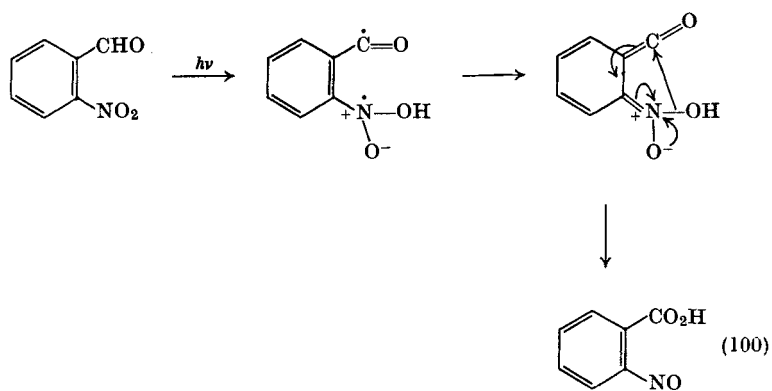
³⁹⁶ P. Pfeiffer, *Ann. Chem.* **411**, 72 (1916); see also P. Pfeiffer and E. Kramer, *Chem. Ber.* **46**, 3655 (1913).

³⁹⁷ R. Huisgen, *Angew. Chem. Intern. Ed. Engl.* **2**, 589 (1963).

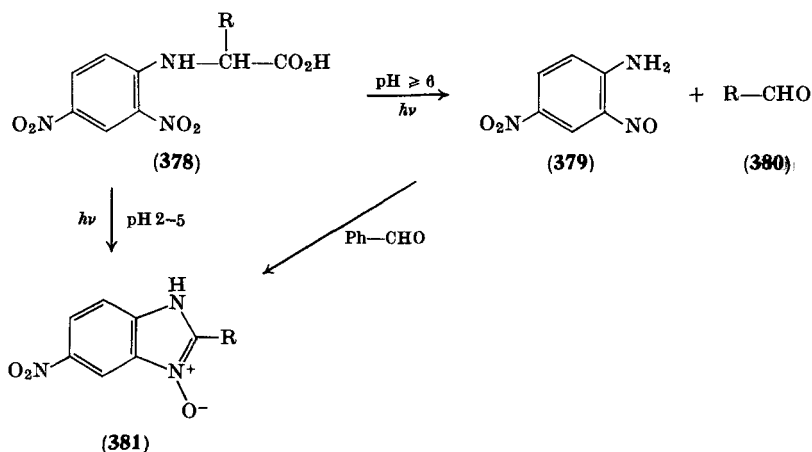
³⁹⁸ J. S. Splitter and M. Calvin, *J. Org. Chem.* **20**, 1086 (1955).

³⁹⁹ D. W. Russell, *J. Chem. Soc.* 894 (1963); D. W. Russell, *Biochem. J.* **87**, 1 (1963).

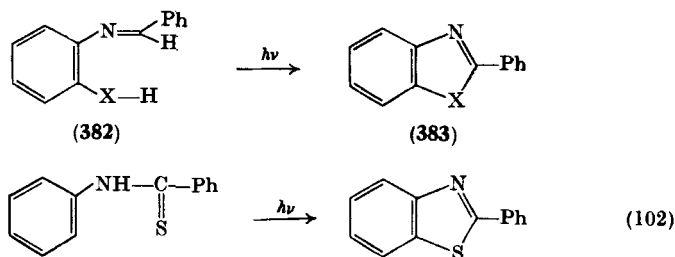
⁴⁰⁰ D. J. Needle and R. J. Pollitt, *J. Chem. Soc., C* 1764 (1967).



related mechanistically to the process described above. At pH 3, irradiation results in the formation of the corresponding 2-substituted 5-nitrobenzimidazole 3-oxide (**381**), and this has been demonstrated for a series of amino acids including glycine ($R = H$) and α -alanine ($R = CH_3$).⁴⁰⁰ It is perhaps significant, however, that 2-phenyl-5-nitrobenzimidazole 3-oxide (**381**; $R = Ph$) can be directly prepared by condensation of 4-nitro-2-nitrosoaniline with benzaldehyde.⁴⁰¹



A few other miscellaneous cyclizations are worthy of mention. *o*-Substituted benzene derivatives of general structure **382** ($X = O, S$ or NH) undergo oxidative cyclization on irradiation to give the corresponding heterocyclic system (**383**).⁴⁰² Similar behavior is exhibited by a thioamide [Eq. (102)]. Nonoxidative photocyclization

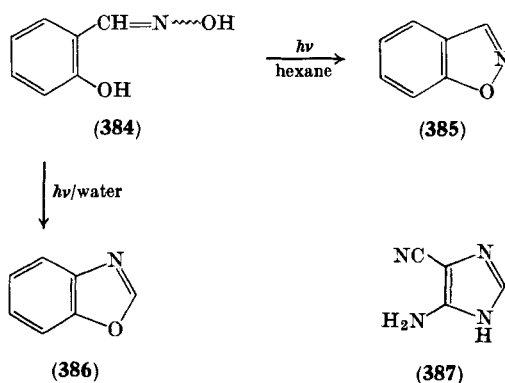


⁴⁰¹ D. W. Russell, *Chem. Commun.* 498 (1965).

⁴⁰² K. H. Grellmann and E. Tauer, *Tetrahedron Letters* 1909 (1967).

occurs in the oxime of salicylaldehyde (**384**), but the process is apparently solvent-dependent. Direct cyclization to benzisoxazole (**385**) occurs in hexane solution, whereas in water, the cyclization is accompanied or preceded by rearrangement and the product is benzoxazole (**386**).⁴⁰²

Finally, 4-cyano-5-aminoimidazole (**387**) is formed by the action of light on the tetramer of HCN in aqueous solution⁴⁰³; the imidazole is easily converted chemically into adenine, thus affording a simple synthesis of this aminopurine.



2. Oxygen Heterocycles

The photoaddition of alcohols and phenols to alkenes has been observed.⁴⁰⁴ The equivalent intramolecular process results in cyclization and the formation of oxygen heterocycles. Irradiation of 2-allyl-4-*t*-butylphenol (**388**) affords 2,3-dihydro-2-methyl-5-*t*-butylbenzofuran (**389**), whereas *o*-3-methylbut-2-enylphenol (**390**) gives 2,2-dimethylchroman (**391**). In both cases, therefore, the addition can be said to occur in a Markovnikov direction.

The irradiation of quercetin pentamethyl ether (**392**) in methanol leads to the formation of four products⁴⁰⁵; the two principal products have been named lumimethylquercetin (**393**) and β -photomethylquercetin (**394**). Excitation of the carbonyl function is followed by

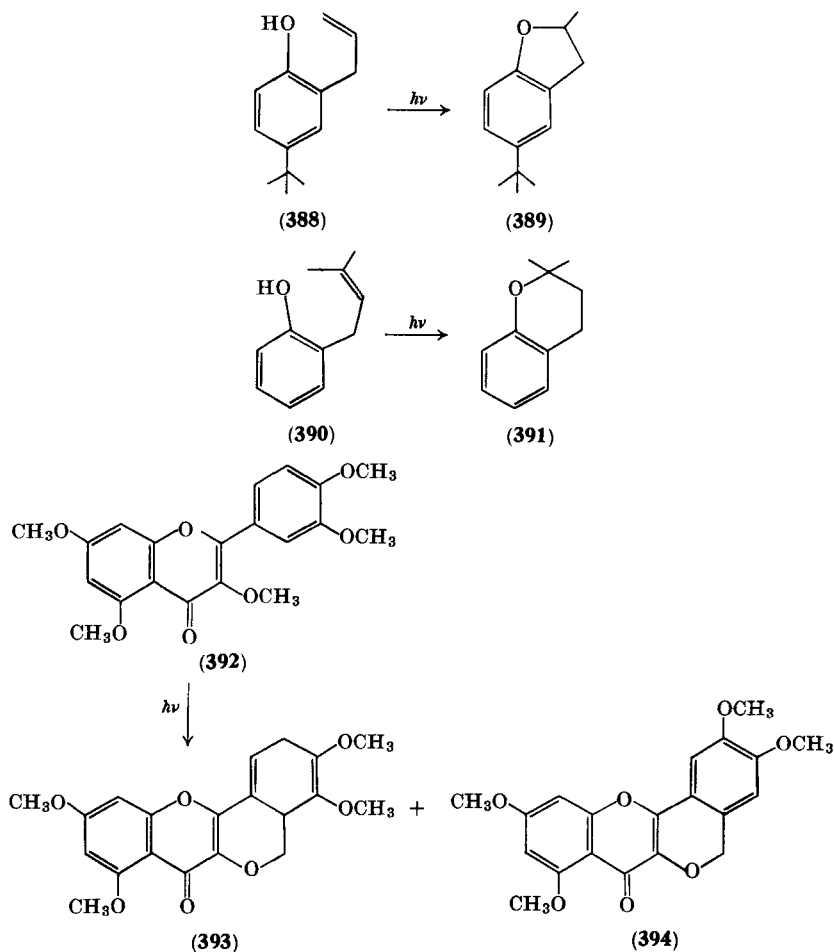
⁴⁰³ J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.* **88**, 1074 (1966).

⁴⁰⁴ W. M. Horspool and P. L. Pauson, *Chem. Commun.* 195 (1967).

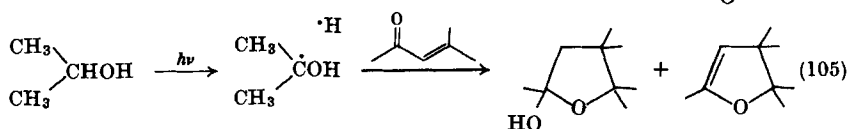
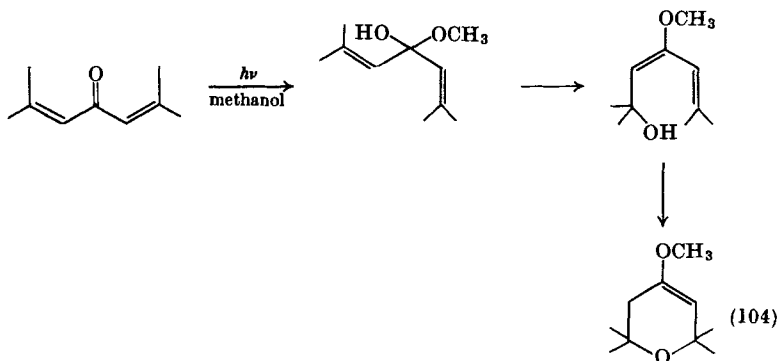
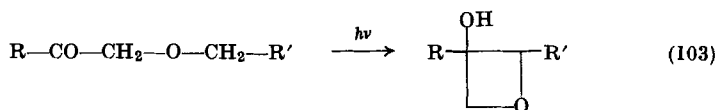
⁴⁰⁵ A. C. Waiss, R. E. Lundin, A. Lee, and J. Corse, *J. Am. Chem. Soc.* **89**, 6213 (1967).

hydrogen abstraction from the adjacent methoxyl group; cyclization of this intermediate leads directly to lumimethylquercetin (**393**). β -Photomethylquercetin (**394**) is not formed by dehydrogenation of lumimethylquercetin.

The photolysis of aldehydes and ketones has been the subject of many investigations, and is adequately dealt with in standard texts on photochemistry. In a few instances, excitation of the carbonyl function can result in cyclization and the formation of heterocyclic systems, although this is usually accompanied by other processes more characteristic of the carbonyl group.



The conversion of aliphatic ketones into substituted cyclobutanols through initial γ -hydrogen abstraction by the excited ketone, followed by cyclization, is a well-documented process. The irradiation of α -alkoxyketones thus offers a useful approach to the synthesis of oxetan-3-ols [Eq. (103)].⁴⁰⁶ The α,β -unsaturated ketone, phorone, undergoes cyclization to a pyran on photolysis in methanol,⁴⁰⁷ but in this case, the reaction mechanism is uncertain. It was suggested that this is the result of photoaddition of methanol to the carbonyl, followed by rearrangement of the hemiacetal and cyclization [Eq. (104)], but as yet there is no decisive evidence to support this. The photoinduced formation of acetals has been reported in aryloxyacetones⁴⁰⁸ and aldehydes.⁴⁰⁹ Mesityl oxide is, however, surprisingly stable under similar conditions.⁴¹⁰ When exposed to light of 184 nm wavelength in isopropanol, reaction is initiated by the photodecomposition of isopropanol and a dihydrofuran and tetrahydrofuran [Eq. (105)] are formed, among other products.



⁴⁰⁶ P. Yates and A. G. Szabo, *Tetrahedron Letters* 485 (1965).

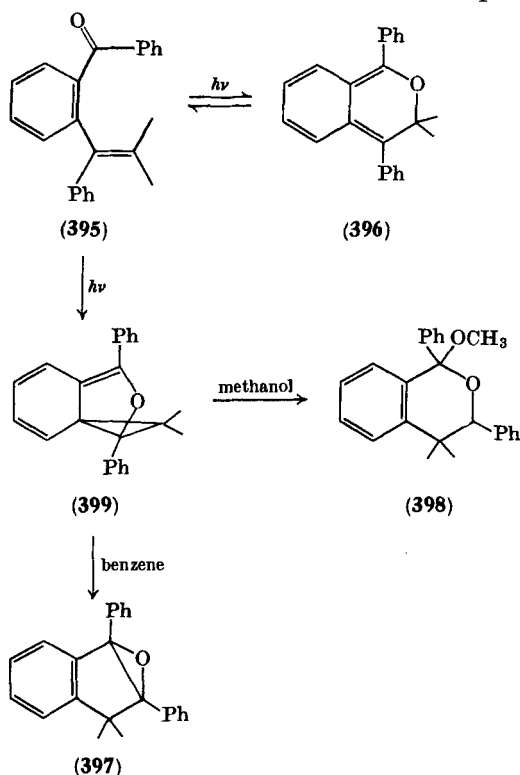
⁴⁰⁷ P. J. Kropp and T. W. Gibson, *J. Chem. Soc., C* 143 (1967).

⁴⁰⁸ M. K. M. Dirania and J. Hill, *J. Chem. Soc., C* 1311 (1968).

⁴⁰⁹ G. Just and C. Pace-Asciak, *Tetrahedron* **22**, 1063 (1966).

⁴¹⁰ N. C. Yang and D-M. Thap, *J. Org. Chem.* **32**, 2462 (1967).

The photoinduced cleavage of *2H*-pyrans to $\alpha,\beta,\gamma,\delta$ -unsaturated ketones, as reported for *2H*-chromene, has already been discussed. The formation of the *2H*-pyran system from such an unsaturated ketone is also known and has been reported for *cis*- β -ionone⁴¹¹ and for the substituted *o*-vinylbenzophenone (395) which on irradiation at low temperature yields the unstable pyran (396).⁴¹² On prolonged photolysis, however, this benzophenone is converted in benzene solution into the epoxide (397) and in methanol solution into the methoxyisochroman (398). It seems probable that a common intermediate exists and that this has the structure 399. A close analogy, therefore, exists between this conversion and the photolysis of *o*-divinylbenzene in which a similar intermediate is postulated.^{413, 414}



⁴¹¹ G. Büchi and N. C. Yang, *J. Am. Chem. Soc.* **79**, 2318 (1957).

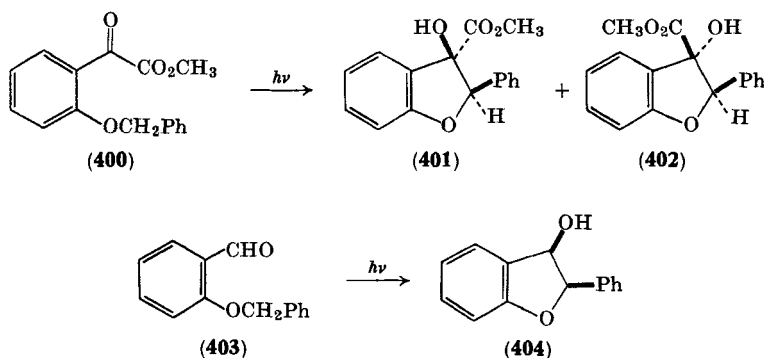
⁴¹² K. R. Huffman and E. F. Ullman, *J. Am. Chem. Soc.* **89**, 5629 (1967).

⁴¹³ M. Pomerantz, *J. Am. Chem. Soc.* **89**, 694 (1967).

⁴¹⁴ J. Meinwald and P. H. Mazzocchi, *J. Am. Chem. Soc.* **89**, 696 (1967).

Other aromatic ketones undergo photocyclization to form oxygen heterocycles. Methyl *o*-benzyloxyphenylglyoxylate (**400**) is converted in high yield into a mixture of the isomers (**401** and **402**).⁴¹⁵ The stereochemistry of the cyclization is both solvent- and temperature-dependent, the former isomer (**401**) being formed almost exclusively in nonpolar solvents such as heptane or benzene, and in each case an excited triplet appears to be involved. The related aldehyde, *O*-benzylsalicylaldehyde (**403**), is similarly converted into *cis*-2-phenyl-3-hydroxy-2,3-dihydrobenzofuran (**404**), but in much lower yield; a second product may possibly be the *trans* isomer.⁴¹⁶

Certain substituted *p*-quinones undergo photoinduced cyclization to give a benzo-fused oxygen heterocycle as a result of $n \rightarrow \pi^*$



excitation. *t*-Butyl-*p*-benzoquinones are converted in this way in acetic acid solution into coumarans⁴¹⁷ [see, for example, Eq. (106)]. Photolysis of 2,5-bisdimethylamino-, 2,5-bispiperidino-, and 2,5-bismorpholino-*p*-benzoquinone in solution similarly affords the corresponding heterocyclic compound⁴¹⁸ [see, for example, Eq. (107)], and benzimidazoles are formed on photolysis in chloroform of *N,N'*-dibenzenesulfonyl-1,4-benzoquinone diimines.⁴¹⁹ The photorearrangement of certain 2-methylaminophenoxaz-3-one derivatives to the

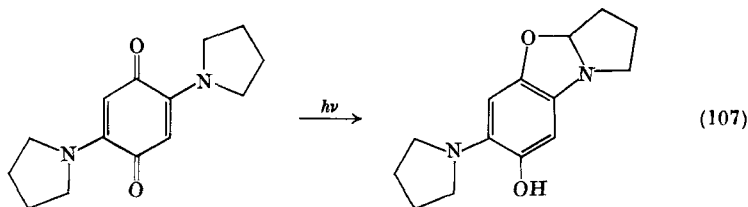
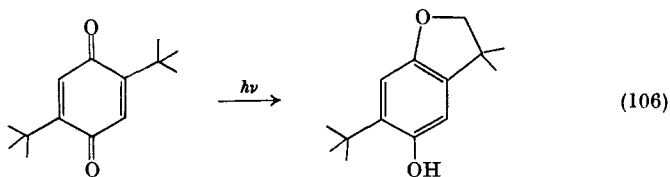
⁴¹⁵ S. P. Pappas, B. C. Pappas, and J. E. Blackwell, *J. Org. Chem.* **32**, 3066 (1967).

⁴¹⁶ S. P. Pappas and J. E. Blackwell, *Tetrahedron Letters* 1171 (1966).

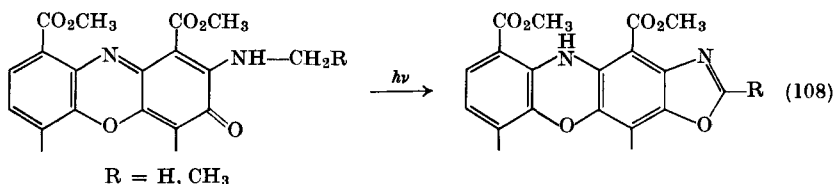
⁴¹⁷ C. M. Orlando, H. Mark, A. K. Bose, and M. S. Manhas, *J. Org. Chem.* **33**, 2512 (1968).

⁴¹⁸ D. W. Cameron and R. G. F. Giles, *J. Chem. Soc., C* 1461 (1968).

⁴¹⁹ I. Baxter and D. W. Cameron, *J. Chem. Soc., C* 1747 (1968).



correspondingly substituted oxazolophenoxazines [Eq. (108)] is presumably the result of an analogous cyclization followed by oxidation.⁴²⁰



The formation of the substituted dibenzofuran-1,4-dione (**405**) from 5,5'-dimethyl-2,2'-di-*p*-benzoquinone (**406**) can be achieved thermally or by photolysis in hydroxylic solvents such as methanol or acetic acid,⁴²¹ and a related cyclization has been observed in dinaphthaquinones.⁴²² A dibenzofuran derivative (**407**) is also obtained on irradiation of the conjugated dione (**408**); the intermediate (**409**) can be isolated by maintaining a temperature of 6° in the reaction flask.⁴²³ A mechanism for the photorearrangement of 2-acetyl-3-furyl-*p*-benzoquinones to derivatives of isobenzofuran has been proposed⁴²⁴ [Eq. (109)].

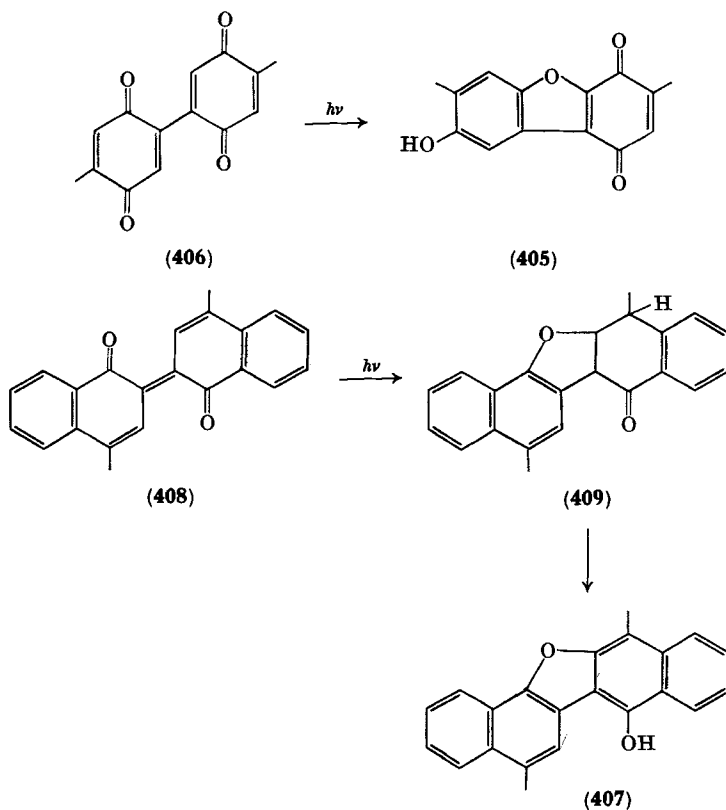
⁴²⁰ S. G. Levine and M. C. Wani, *J. Org. Chem.* **30**, 3185 (1965).

⁴²¹ A. J. Shand and R. H. Thomson, *Tetrahedron* **19**, 1919 (1963).

⁴²² D. Schulte-Frohlinde and V. Werner, *Chem. Ber.* **94**, 2726 (1961).

⁴²³ D. Schulte-Frohlinde, *Chem. Ber.* **94**, 2382 (1961).

⁴²⁴ C. Weisgerber and C. H. Eugster, *Helv. Chim. Acta* **49**, 1806 (1966).



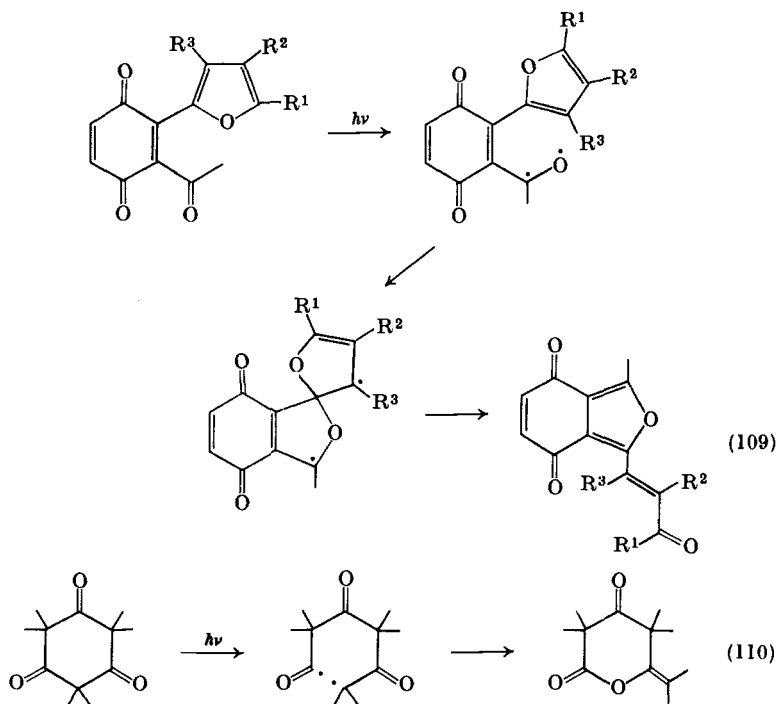
The photolysis of cyclic ketones, in general, results in homolytic cleavage of the carbon-carbon bond adjacent to the carbonyl function. For details of this process, the reader is referred to the review by Srinivasan.⁴²⁵ Included among the photoproducts are certain oxygen heterocycles, formed by cyclization of reactive intermediates. Thus, cleavage in a cyclic β -diketone, such as tetramethylcyclobutane-1,3-dione or hexamethylcyclohexane-1,3,5-trione [Eq. (110)] is followed by cyclization on the oxygen atom to form a lactone.^{426, 427} γ -Lactone formation is also observed on photolysis of 2,2-diphenylindane-1,3-dione [Eq. (111)] in ether, and the process is reversible.⁴²⁸

⁴²⁵ R. Srinivasan, *Advan. Photochem.* **1**, 83 (1963).

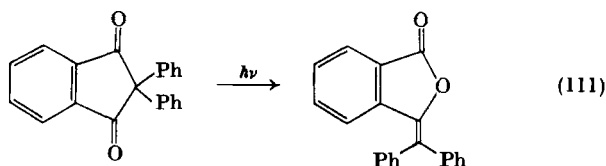
⁴²⁶ R. C. Cookson, A. G. Edwards, J. Hudec, and M. Kingsland, *Chem. Commun.* **98** (1965).

⁴²⁷ H. U. Hostettler, *Tetrahedron Letters* 1941 (1965).

⁴²⁸ J. Rigaudy and P. Derible, *Bull. Soc. Chim. France* 3047 (1965).



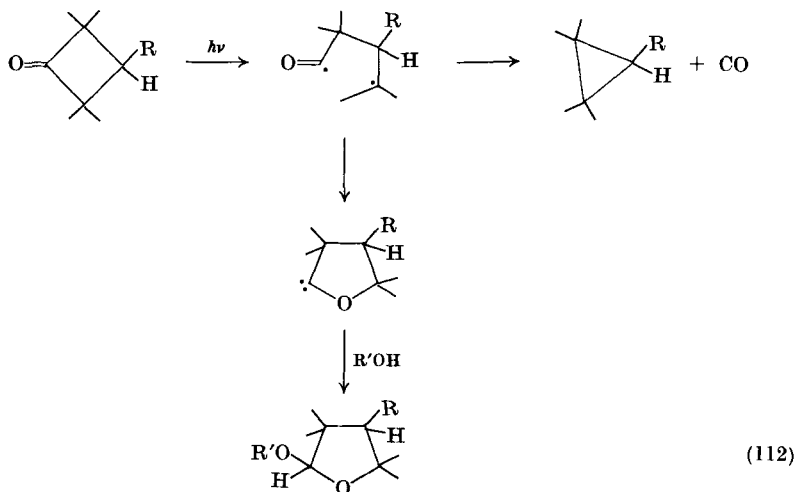
A series of substituted 2,2,4,4-tetramethylcyclobutanones in which the substituent is alkyl, aryl, hydroxy, amino, or imino yield on photolysis in methanol or ethanol the corresponding alkoxytetrahydrofuran [Eq. (112)] in addition to a cyclopropane derivative formed by decarbonylation.⁴²⁹ Earlier examples of this process occurring in 7,7-dimethyl[3.2.0]bicyclohept-2-en-6-one⁴³⁰ and in (+)-cyclocamphanone⁴³¹ have been reported. In all cases, intramolecular hydrogen abstraction is unfavorable, and a carbene is postulated as the intermediate species.



⁴²⁹ H. U. Hostettler, *Helv. Chim. Acta* **49**, 2417 (1966).

⁴³⁰ H. U. Hostettler, *Tetrahedron Letters* 687 (1965).

⁴³¹ P. Yates and L. Kilmurry, *Tetrahedron Letters* 1739 (1964).



VII. Photooxidation of Heterocycles

The literature on photooxidations is extensive, and comprehensive coverage is beyond the scope of this review. For further information, the reader is referred to the work of Gollnick and Schenck,^{432, 433} and the text by Neckers.⁴³⁴ The mechanism has also been the subject of much investigation, and singlet oxygen, formed by excitation of ground-state triplet oxygen, is thought to be involved.

Photolysis, in the presence of oxygen, of alkenes containing an allylic hydrogen atom leads to the formation of hydroperoxides. The sensitized process is more efficient, and often yields photoproducts different in structure from those obtained by nonsensitized photooxidation. Cyclohexadiene and related dienes on photolysis in the presence of oxygen yield the transannular peroxides. Thus, on photosensitized oxidation, α -terpinene (**410**) is converted into ascaridole (**411**).⁴³⁵ The equivalent process is not, in general, observed in acyclic dienes. Certain polynuclear aromatic hydrocarbons, such as anthracene and naphthacene and including the heterocycles 5,10-diphenyl-1-

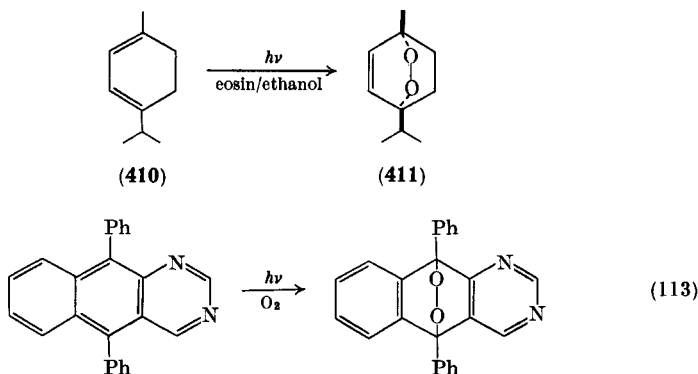
⁴³² K. Gollnick, *Advan. Photochem.* **6**, 1 (1968).

⁴³³ K. Gollnick and G. O. Schenck, in "1,4-Cycloaddition Reactions" (J. Hamer, ed.), p. 255. Academic Press, New York, 1967.

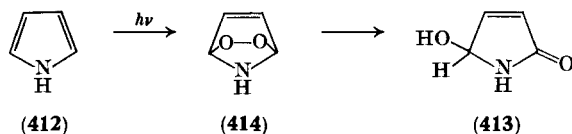
⁴³⁴ D. C. Neckers, "Mechanistic Organic Photochemistry," p. 148. Reinhold, New York, 1967.

⁴³⁵ G. O. Schenck and K. Ziegler, *Naturwissenschaften* **32**, 157 (1944).

azaanthracene,⁴³⁶ 5,10-diphenyl-2-azaanthracene,⁴³⁷ 3,4-benzo-5-azanaphthacene,⁴³⁸ and 5,10-diphenylbenzo[*g*]quinazoline⁴³⁹ [Eq. (113)], also form transannular peroxides.



Photosensitized photooxidation of pyrrole (412) by irradiation in the presence of eosin gives rise to the photoproduct (413), presumably via the intermediate peroxide (414).⁴⁴⁰ Transannular peroxides are



similarly involved in the photosensitized oxidation of imidazoles⁴⁴¹ and purines.^{442, 443} The sensitized photooxidation of furan and its simple derivatives has been more thoroughly investigated.⁴³³ Furan (415), on irradiation at -90° yields the unstable peroxide (416) which is converted in methanol into the pseudoester (417); the same pseudoester is formed on photosensitized oxidation of furan in methanol at

⁴³⁶ A. Étienne, *Ann. Chim. (Paris)* [12] **1**, 5 (1946).

⁴³⁷ A. Étienne and J. Robert, *Compt. Rend.* **223**, 331 (1946).

⁴³⁸ A. Étienne and A. Staehelin, *Bull. Soc. Chim. France* 748 (1954).

⁴³⁹ M. Legrand, *Compt. Rend.* **237**, 822 (1953).

⁴⁴⁰ P. de Mayo and S. T. Reid, *Chem. Ind. (London)* 1576 (1962).

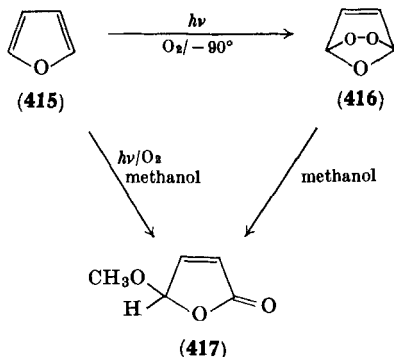
⁴⁴¹ H. H. Wasserman, K. Stiller, and M. B. Floyd, *Tetrahedron Letters* 3277 (1968).

⁴⁴² T. Matsuura and I. Saito, *Chem. Commun.* 693 (1967).

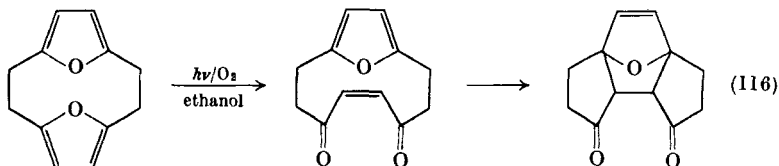
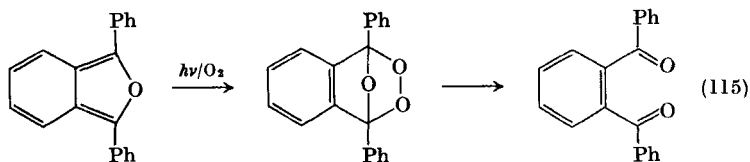
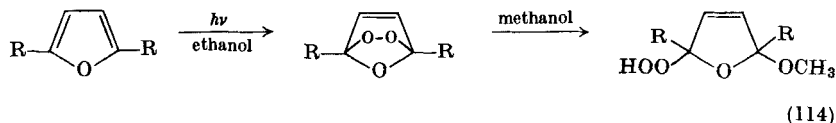
⁴⁴³ T. Matsuura and I. Saito, *Tetrahedron Letters* 3273 (1968).

room temperature. The corresponding pseudoacid is obtained in inert solvents.

Analogous oxidations have been reported in 2-methylfuran and 2,5-dimethylfuran. In addition, irradiation in methanol of these two



furans yields the corresponding methoxyhydroperoxy-2,5-dihydrofurans [Eq. (114)]; the same hydroperoxides are obtained by reaction of the peroxide with methanol. The peroxide has been isolated as an intermediate in the conversion of 1,3-diphenylisobenzofuran into *o*-dibenzoylbenzene [Eq. (115)],⁴⁴⁴ and a peroxide has also been obtained from 1,2,3-triphenylisindole.⁴⁴⁵ Analogous species are

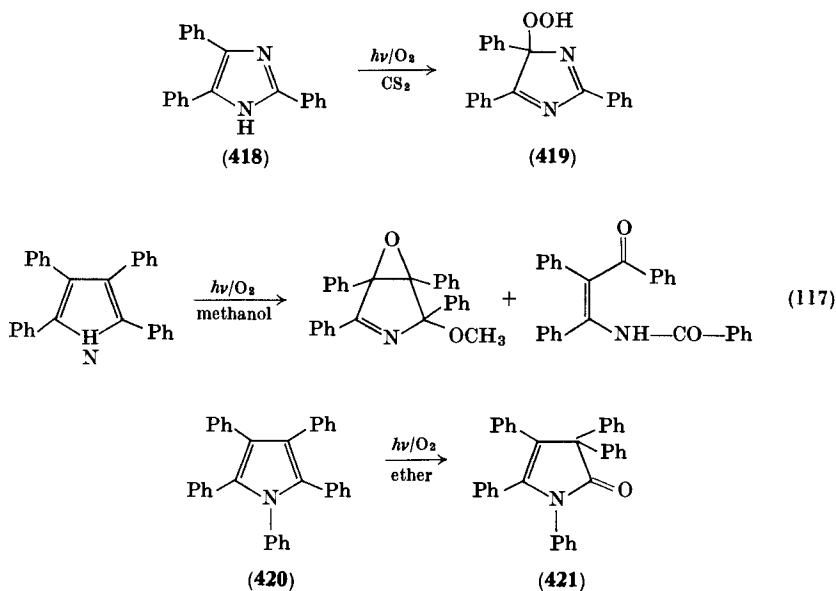


⁴⁴⁴ C. Dufraisse and S. Ecary, *Compt. Rend.* **223**, 735 (1946).

⁴⁴⁵ W. Theilacker and W. Schmidt, *Ann. Chem.* **605**, 43 (1957).

thought to be implicated in the photooxidation of 2- and 5-aryl-furans⁴³³ and in the photooxidation of a furanocyclophane [Eq. (116)].⁴⁴⁶ Other furanocyclophanes have been studied.⁴⁴⁷

The photochemical oxidation of other heterocycles has been interpreted in terms of intermediate hydroperoxides. Thus, for example, 2,4,5-triphenylimidazole (**418**) forms^{448, 449} the stable hydroperoxide (**419**), and hydroperoxides are probably involved in the photooxidation of 2,3-diethylindole,⁴⁵⁰ 2,3,4,5-tetraphenylpyrrole [Eq. (117)],⁴⁵¹ and 2,3,4,5-tetraphenylfuran.⁴⁵¹ Pentaphenylpyrrole (**420**) is converted into the lactam (**421**), presumably by rearrangement of the intermediate peroxide.⁴⁵²



⁴⁴⁶ H. H. Wasserman and A. R. Doumaux, *J. Am. Chem. Soc.* **84**, 4611 (1962).

⁴⁴⁷ H. H. Wasserman, A. R. Doumaux, and R. E. Davis, *J. Am. Chem. Soc.* **88**, 4517 (1966).

⁴⁴⁸ J. Sonnenberg and D. M. White, *J. Am. Chem. Soc.* **86**, 5685 (1964).

⁴⁴⁹ E. H. White and M. J. C. Harding, *J. Am. Chem. Soc.* **86**, 5686 (1964).

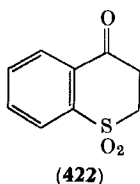
⁴⁵⁰ E. Leete, *J. Am. Chem. Soc.* **83**, 3645 (1961).

⁴⁵¹ H. H. Wasserman and A. Liberles, *J. Am. Chem. Soc.* **82**, 2806 (1960).

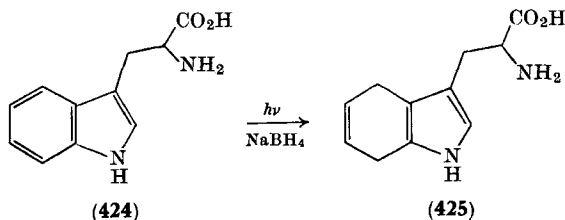
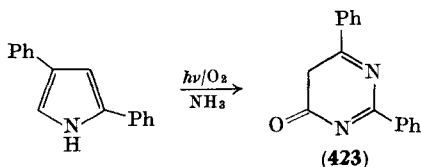
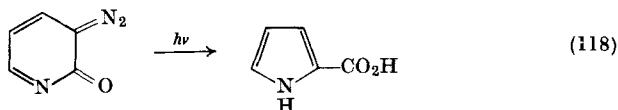
⁴⁵² C. Dufraisse, G. Rio, and A. Ranjon, *Compt. Rend.* **C265**, 310 (1967).

VIII. Conclusion

This review has been concerned with the photochemistry of heterocyclic systems; photoreactions which are more correctly designated as reactions of functional groups have, in general, been omitted or not seriously considered. Thus, the formation of pinacols by the photo-reduction of such heterocyclic ketones as 3-acetylpyridine⁴⁵³ and the keto sulfone (422)⁴⁵⁴ has not been included, nor has *cis-trans* isomerization been reviewed.



A number of other general photochemical reactions have been applied to heterocyclic systems, and these are worthy of mention. *o*-Quinone diazides on irradiation undergo ring contraction with loss of nitrogen to give a carboxylic acid; this has been observed in a



⁴⁵³ W. L. Bencze, C. A. Burekhardt, and W. L. Yost, *J. Org. Chem.* **27**, 2865 (1962).

⁴⁵⁴ I. W. J. Still and M. T. Thomas, *J. Org. Chem.* **33**, 2730 (1968).

number of heterocyclic systems⁴⁵⁵ [see, for example, Eq. (118)]. Ring enlargement of 5-membered heterocycles by irradiation in the presence of ammonia and oxygen is also known to occur,⁴⁵⁵ and is exemplified in the conversion of 2,4-diphenylpyrrole into the pyrimidone (**423**).

Finally, the light-catalyzed sodium borohydride reductions of certain heterocycles are of considerable interest; tryptophan (**424**), for example, is converted into the dihydrotryptophan (**425**).⁴⁵⁶

⁴⁵⁵ A. Mustafa, *Advan. Photochem.* **2**, 63 (1964).

⁴⁵⁶ O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Am. Chem. Soc.* **88**, 3941 (1966).

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The Naphthyridines

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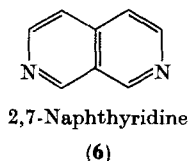
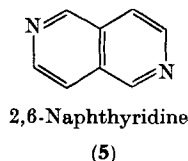
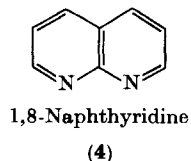
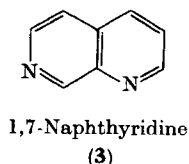
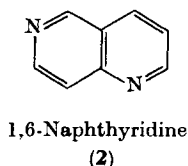
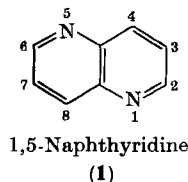
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I. Introduction

The naphthyridines consist of a group of six diazanaphthalenes with one nitrogen atom in each ring and none at a bridgehead position. The six possible isomers (1–6) are numbered as indicated.



These compounds have also been called pyridopyridines and benzodiazines. The early literature describes 1,5-naphthyridine as isonaphthyridine and the 1,6-isomer as 2,6-naphthyridine. Prior to 1950, the 2,7-naphthyridines were referred to as derivatives of copyrine. Fortunately, the nomenclature has now been standardized and much of the confusion has been eliminated.

Naphthyridine chemistry has been well reviewed by Allen¹ (up to 1947), and by Weiss and Hauser² (up to 1958). It has also been considered incidentally by Duffin³ (quaternization reactions) and by Campbell⁴ in "The Chemistry of Carbon Compounds."

The first derivative of the naphthyridine ring system was prepared by Reissert⁵ in 1893, who suggested the use of the name. No unsubstituted naphthyridine was known until 1926, when 1,5-naphthyridine⁶

¹ C. F. H. Allen, *Chem. Rev.* **47**, 275 (1950).

² M. J. Weiss and C. R. Hauser, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, pp. 198–236. Wiley, New York, 1961.

³ G. F. Duffin, *Advan. Heterocyclic Chem.* **3**, 46 (1964).

⁴ N. Campbell, in "The Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. 4B, pp. 1035–1038. Elsevier, Amsterdam, 1959.

⁵ A. Reissert, *Chem. Ber.* **26**, 2137 (1893).

⁶ B. Bobranski and E. Sucharda, *Chem. Ber.* **60**, 1081 (1926).

and 1,8-naphthyridine⁷ were prepared. The 1,6-,⁸ 1,7,⁹ and the 2,7-naphthyridines¹⁰ were prepared in 1958 by Ikekawa. Albert¹¹ reported the synthesis of 1,6- and 1,7-naphthyridine in 1960, unaware of Ikekawa's earlier work. Recently, two papers^{12, 13} have reported independent syntheses of the last unknown isomer, 2,6-naphthyridine.

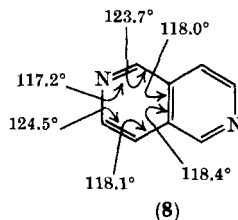
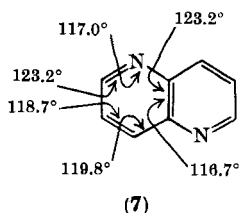
The aim of this review is to report on advances in naphthyridine chemistry since about 1958.

II. Physical Properties

A. CRYSTAL STRUCTURE

The parent naphthyridines are crystalline (see Table I) and some X-ray crystallographic work^{14, 15} has been reported for the 1,5- and the 2,6-naphthyridines.

The bond lengths (see Table II) and the bond angles of these two compounds (**7** and **8**) have been determined as their dihydrates. The 1,5-naphthyridine can be obtained in two crystalline forms, rhombic and monoclinic, by sublimation at 30° and 35°, respectively. Both forms lose water at 38°–40°.



⁷ G. Koller, *Chem. Ber.* **60**, 1918 (1927).

⁸ N. Ikekawa, *Chem. Pharm. Bull. (Tokyo)* **6**, 263 (1958).

⁹ N. Ikekawa, *Chem. Pharm. Bull. (Tokyo)* **6**, 401 (1958).

¹⁰ N. Ikekawa, *Chem. Pharm. Bull. (Tokyo)* **6**, 269 (1958).

¹¹ A. Albert, *J. Chem. Soc.* 1790 (1960).

¹² G. Giacomello, F. Gualtieri, F. M. Ricciari, and M. L. Stein, *Tetrahedron Letters* 1117 (1965).

¹³ R. Tan and A. Taurins, *Tetrahedron Letters* 2737 (1965).

¹⁴ M. Brufani, D. Duranti, and G. Giacomello, *Gazz. Chim. Ital.* **89**, 2328 (1959); *Chem. Abstr.* **55**, 5081 (1961).

¹⁵ M. Brufani, W. Fedeli, G. Giacomello, F. M. Ricciari, and A. Vaciano, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **40**, 187 (1966); *Chem. Abstr.* **65**, 11464 (1966).

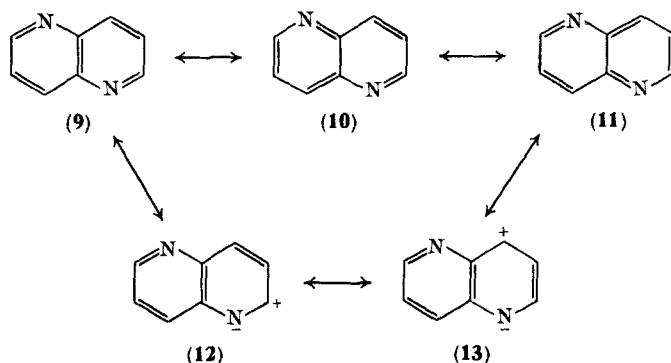
TABLE I
SOME PROPERTIES OF THE NAPHTHYRIDINES

Naphthyridine	Melting point (°C)	Ref.	Melting point of picrate (°C)	Ref.
1,5-	75 ^a	16	200	6
1,6-	35–36 ^b	17	219–220	8
1,7-	64	16	195.5–196.5	18
			205–206	9
1,8-	98–99	18	207–208	7
2,6-	118–119	14	206	13
2,7-	92–94	10	240	10

^a Boiling point 150°–152°/54 mm.

^b Twice sublimed sample. This melting point is higher than earlier reported.

The bond lengths of these two naphthyridines confirm that some “bond fixation” occurs. We can predict that the extent of this fixation will be roughly the same in the remaining naphthyridines. An examination of the bond-length changes that take place (see Table II) in the transition from benzene to naphthalene and from pyridine to the naphthyridines shows nearly the same degree of bond shortening and lengthening in both bicyclic systems. The “fixation” is also evident in the 1,2 C–N bonds in the naphthyridines which are shorter than the

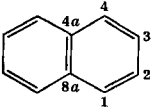
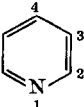
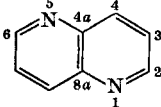
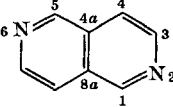


¹⁶ H. Rapoport and A. D. Batcho, *J. Org. Chem.* **28**, 1753 (1963).

¹⁷ W. W. Paudler and T. J. Kress, unpublished results.

¹⁸ R. Tan and A. Taurins, *Tetrahedron Letters* 1233 (1966).

TABLE II
BOND LENGTH DATA^a

					
Compound	Bond ^b	Naphthalene	Pyridine	1,5-Naphthyridine	2,6-Naphthyridine
1,2 Bond	C-C	1.37	—	—	—
	C-N	—	1.34	1.31	1.31
2,3 Bond	C-C	1.40	1.39	1.41	—
	C-N	—	—	—	—
3,4 Bond	C-C	1.37	1.40	1.36	1.37
Bridge 4a-8a	C-C	1.39	—	1.41	1.40
4-4a Bond	C-C	1.43	—	1.42	1.42
1-8a Bond	C-C	1.43	—	—	1.41
	C-N	—	—	1.36	—

^a Data in ångstroms.

^b Single C-C 1.54 Å; olefin C-C 1.34 Å; and benzene C-C 1.39 Å.

corresponding bond in pyridine. Although, for example, in 1,5-naphthyridine, canonical structure **9** and to a smaller extent structures **10** and **11** are probably the major contributors to the ground state, the charged structures **12** and **13** must also be included to account for the chemical properties of the naphthyridines.

B. QUANTUM CHEMICAL CALCULATIONS

During the past 20 years several groups of workers¹⁹⁻²⁸ have carried out quantum mechanical calculations on the naphthyridines and have correlated the results with various chemical and physical properties.

A number of correlations have been made, with moderate success, between the transition energies and intensities in the ultraviolet (UV)

TABLE III
TOTAL π -ENERGIES AND DELOCALIZATION ENERGIES OF
THE NAPHTHYRIDINES^a

Compound	E_{π} total	Delocalization energy (β)
Naphthalene	$10\alpha + 13.68\beta$	3.68
1,5-Naphthyridine	$10\alpha + 16.37\beta$	3.81
1,6-Naphthyridine	$10\alpha + 16.37\beta$	3.81
1,7-Naphthyridine	$10\alpha + 16.34\beta$	3.78
1,8-Naphthyridine	$10\alpha + 16.41\beta$	3.85
2,6-Naphthyridine	$10\alpha + 16.32\beta$	3.76
2,7-Naphthyridine	$10\alpha + 16.35\beta$	3.79

^a $\alpha_{\text{CN}} = \alpha_{\text{C}} + 1.1\beta$, $\beta_{\text{CN}} = 1.0\beta_{\text{CC}}$ [as described in W. W. Paudler and T. J. Kress, *J. Org. Chem.* **33**, 1384 (1968)].

¹⁹ T. E. Peacock, *J. Chem. Soc.* 1946 (1960).

²⁰ S. F. Mason, *J. Chem. Soc.* 493 (1962).

²¹ S. C. Wait and J. W. Wesley, *J. Mol. Spectry.* **19**, 25 (1966).

²² T. J. Kress, Ph.D. Thesis, Ohio University, Athens, Ohio (1967).

²³ A. H. Gawer and B. P. Dailey, *J. Chem. Phys.* **43**, 2658 (1965).

²⁴ W. W. Paudler and T. J. Kress, *J. Org. Chem.* **33**, 1384 (1968).

²⁵ V. Oakes and H. N. Rydon, *J. Chem. Soc.* 204 (1958).

²⁶ H. C. Longuet-Higgins and C. A. Coulson, *J. Chem. Soc.* 971 (1949).

²⁷ S. Basu and R. Bhattacharya, *Proc. Natl. Inst. Sci. India A23*, 1 (1957); *Chem. Abstr.* **52**, 864 (1958).

²⁸ J. C. Henning, *J. Chem. Phys.* **44**, 2139 (1966).

spectra of the naphthyridines and the energy of the lowest lying unoccupied molecular orbital.¹⁹⁻²¹

The total π energy and the delocalization energy of the naphthyridines have been compared with naphthalene (cf. Table III).^{22, 24} The results of this study suggested that the naphthyridines have similar resonance energies.

The distribution of π electrons in the naphthyridines has been calculated using several sets of parameters.^{24, 26} Correlations between total π -electron densities with electrophilic²⁴ and nucleophilic^{24, 25} substitution and hyperfine splitting constants²⁸ have been made with some success.

C. SPECTRA

1. *Infrared Spectra*

As a result of a study of the infrared spectra of all the 1, x -diazanaphthalenes ($x = 2$ to 8), Armarego and co-workers²⁹ concluded that no correlation between spectral band position and the arrangement of one, two, or three adjacent hydrogen atoms could be made in these spectra. This is contrary to the results of earlier publications^{17, 30} which attempted to correlate the out-of-plane vibrations (650–1000 cm^{-1}) with the pattern of substitution in the naphthyridines. These studies had led to the assignments of absorption peaks at 860–900 cm^{-1} for an isolated hydrogen, 830–850 cm^{-1} for two adjacent hydrogens, and 760–820 cm^{-1} for three adjacent hydrogens. In view of the results of Armarego *et al.*, these assignments should be utilized with caution since they show, in fact, a wide variation from one naphthyridine isomer to another. This variation, however, is less marked when comparing a series of compounds of the same isomer.

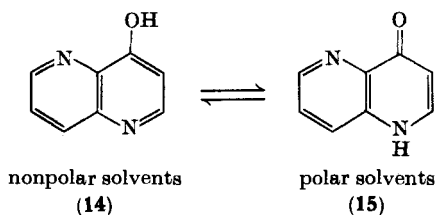
A complete assignment of the characteristic absorption bands of a series of 1,5-naphthyridines has been reported by Czuba³¹ who compared the spectrum of 1,5-naphthyridine with that of a 5-substituted quinoline.

²⁹ W. L. F. Armarego, G. B. Barlin, and E. Spinner, *Spectrochim. Acta* **22**, 117 (1966).

³⁰ N. Ikekawa, *Chem. Pharm. Bull. (Tokyo)* **6**, 404 (1958); *Chem. Abstr.* **53**, 3227 (1959).

³¹ W. Czuba, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **11**, 423 (1963); *Chem. Abstr.* **60**, 2454 (1964).

The keto-enol tautomerism in 4-hydroxy-1,5-naphthyridine (**14**) has been studied spectroscopically in solution and in the solid state.³² The keto form (**15**) is said to predominate in polar solvents and the enol form (**14**) in nonpolar solvents.



The infrared absorption bands of the carbonyl and the N-H stretching regions have been reported for several other hydroxy-naphthyridines, although no conclusion was offered as to the position of a possible keto-enol tautomerism.^{33, 34}

Several 2,4,7-trisubstituted 1,8-naphthyridine spectra have been analyzed and the ring-stretching frequencies have been assigned.³⁵

2. Phosphorescence Spectra

The phosphorescence spectrum of 1,5-naphthyridine is similar to that of naphthalene.³⁶

3. UV Spectra

The UV spectra of the six naphthyridines are listed in Table IV. The 1,5- and 1,8-naphthyridine, as well as the 1,6- and 1,7-naphthyridine spectra, strongly resemble one another.¹¹ The spectra of the 2,6- and 2,7-naphthyridines, on the other hand, neither resemble each

³² D. N. Bailey, D. M. Hercules, and T. D. Eck, *Anal. Chem.* **39**, 877 (1967).

³³ S. F. Mason, *J. Chem. Soc.* 4874 (1957).

³⁴ F. J. C. Rossotti and H. S. Rossotti, *J. Chem. Soc.* 1304 (1958).

³⁵ J. Schurz, A. Ullrich, and H. Bayzer, *Monatsh. Chem.* **90**, 29 (1959).

³⁶ R. Mueller and F. Doerr, *Z. Elektrochem.* **63**, 1150 (1959).

other nor are they similar to any other naphthyridine. In general, the 1,*x*-naphthyridine (*x* = 5, 6, 7, or 8) spectra consist of three distinct bands similar to those of quinoline and isoquinoline.

A detailed analysis of the UV spectra of 4-hydroxy-1,5-naphthyridine,³² and of a large number of substituted 1,8-naphthyridines³⁷ has been reported. Numerous individual spectra have been described, but a detailed discussion is beyond the scope of this review.

TABLE IV
ULTRAVIOLET SPECTRA OF THE NAPHTHYRIDINES^a

Naphthyridine	λ_{\max} , m μ (log ϵ)	Ref.
1,5-	250 (3.65), 259 (3.63), 268 (3.51), 297 (3.75), 304 (3.79), 309 (3.78)	16
1,6-	220 (4.43), 248 (3.62), 303 (3.54), 314 (3.49)	8
1,7-	219 (4.42), 262 (3.58), 302 (3.33), 314 (3.28)	16
1,8-	257 (3.60), 295 (3.65), 302 (3.79), 307 (3.80)	17
2,6-	247 (3.34), 255 (3.42), 264 (3.33), 318 (3.34), 330 (3.30)	12
2,7-	274 (3.61), 292 (3.49), 298 (3.43), 305 (3.42)	10

^a In methanol.

4. Nuclear Magnetic Resonance Spectra

The proton magnetic resonance (PMR) spectra of all parent compounds except the 2,7-isomer have been determined. All the spectra can be interpreted by first-order splitting rules including cross-ring and *para* spin-spin coupling. The various chemical shifts and coupling constants are listed in Table V.

The use of PMR spectroscopy in the structure determination of a large number of naphthyridines has greatly facilitated investigations involving cyclizations and substitution reactions.

The spectra of the many naphthyridine derivatives that have been reported are too numerous to list individually. The references in Table V can be used as guides leading to more complete compilations.

³⁷ W. Skoda and H. Bayzer, *Monatsh. Chem.* **89**, 5 (1958).

TABLE V
PMR SPECTRAL DATA OF VARIOUS NAPHTHYRIDINES

Compound	Solvent	Chemical shift (τ)								Refs. to derivatives
		H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈	
1,5-Naphthyridine	CDCl ₃	—	1.03	2.42	1.60	—	1.03	2.42	1.60	23, 24, 38–44
1,6-Naphthyridine	CDCl ₃	—	0.90	2.48	1.72	0.72	—	1.24	2.07	24, 38–44
1,7-Naphthyridine	CDCl ₃	—	0.86	2.33	1.74	2.28	1.27	—	0.34	24, 38, 42–45
1,8-Naphthyridine	CDCl ₃	—	0.78	2.52	1.78	1.78	2.52	0.78	—	24, 40–44, 46–48
2,6-Naphthyridine	CDCl ₃	0.61	—	1.25	2.22	0.61	—	1.25	2.22	12, 13

Compound	Coupling constants J (cps)										
	2,3	2,4	3,4	4,8	5,6	5,7	5,8	6,7	6,8	7,8	
1,5-Naphthyridine	4.1	1.8	8.0	0.6	—	—	—	4.1	1.8	8.0	
1,6-Naphthyridine	4.1	1.9	8.2	0.9	—	—	0.9	—	—	6.0	
1,7-Naphthyridine	4.2	1.6	8.4	0.9	5.6	—	0.9	—	—	—	
1,8-Naphthyridine	4.2	2.0	8.0	—	8.0	2.0	—	4.2	—	—	
2,6-Naphthyridine	—	—	6.0	—	—	—	—	—	—	6.0	

5. Mass Spectra

All four parent 1,5-, 1,6-, 1,7-, and 1,8-naphthyridines afford essentially identical mass spectra (see Fig. 1).⁴⁹ The three most abundant fragment ions in their spectra are found at (a) m/e 103, the ion resulting from direct expulsion of HCN from the molecular ion,

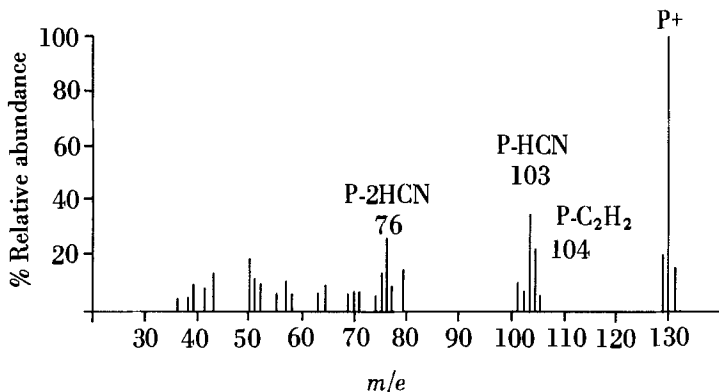


FIG. 1. Mass spectra of the 1,*x*-naphthyridines.

(b) m/e 104, the fragment formed by loss of C_2H_2 from the parent ion-radical, and (c) m/e 76 obtained from the m/e 103 ion by loss of another molecule of HCN.

The mass spectra of the 2-, 3-, and 4-monomethyl-1,5-, 1,6-, and 1,8-naphthyridines, seven dimethyl-1,8-naphthyridines, and one trimethyl-1,8-naphthyridine have also been reported. The major fragmentation pathways for the various parent and methyl-substituted naphthyridines can be summarized by the following general statements.

- ³⁸ W. W. Paudler and T. J. Kress, *Chem. Ind. (London)* 1557 (1966).
- ³⁹ W. W. Paudler and T. J. Kress, *J. Heterocyclic Chem.* **2**, 393 (1965).
- ⁴⁰ W. W. Paudler and T. J. Kress, *J. Org. Chem.* **31**, 3055 (1966).
- ⁴¹ W. W. Paudler and T. J. Kress, *J. Heterocyclic Chem.* **4**, 284 (1967).
- ⁴² W. W. Paudler and T. J. Kress, *J. Heterocyclic Chem.* **5**, 561 (1968).
- ⁴³ W. L. F. Armarego and T. Batterman, *J. Chem. Soc., B* 750 (1966).
- ⁴⁴ W. L. F. Armarego, *J. Chem. Soc., C* 377 (1967).
- ⁴⁵ W. W. Paudler and T. J. Kress, *J. Org. Chem.* **32**, 2616 (1967).
- ⁴⁶ W. W. Paudler and T. J. Kress, *J. Org. Chem.* **32**, 832 (1967).
- ⁴⁷ E. M. Hawes and D. G. Wibberley, *J. Chem. Soc., C* 315 (1966).
- ⁴⁸ E. M. Hawes and D. G. Wibberley, *J. Chem. Soc., C* 1564 (1967).
- ⁴⁹ W. W. Paudler and T. J. Kress, *J. Heterocyclic Chem.* **4**, 547 (1967).

1. The loss of HCN from either the molecular ion or the P-1 ring-expanded ion in the case of the methyl derivatives is significant in all examples studied.

2. The loss of a methyl group is significant only from the 2- and the 4-positions.

3. The loss of hydrogen from a methyl group occurs in all methyl compounds.

4. The loss of C_2H_2 from the molecular ion occurs when the C-3 and C-4 positions are unsubstituted.

5. The ring expansion of the benzyl-type cations occurs in these methyl compounds regardless of the position of the nitrogen atoms with respect to the methyl group in either ring.

These fragmentation processes are similar to observations made on the quinolines.

The electron-impact-induced fragmentations of two dibenzo[*b,f*]-1,6-naphthyridines,⁵⁰ several benzo[*f*]1,7-naphthyridines,⁴⁵ and some perhydro tricyclic homologs of 1,6- and 2,7-naphthyridine⁵¹ follow expected breakdown pathways.

D. IONIZATION PROPERTIES

The basic strengths of the parent naphthyridines (cf. Table VI) are lower than those of quinoline (4.94) and isoquinoline (5.40). This has been attributed to the relayed inductive effect of one doubly bonded nitrogen atom to the other. It was suggested¹¹ and later confirmed⁵⁶ that the greater basic strength of the 1,6- and the 1,7-isomers as compared to the 1,5- and the 1,8-compounds indicates that protonation occurs on N-6 and N-7, respectively, rather than on N-1 (compare the pK_a of quinoline with that of isoquinoline).¹¹

It is of interest to compare the pK_a 's of the various hydroxy-naphthyridines listed in Table VI. The 4-hydroxy-1,5- and the 8-hydroxy-1,7-naphthyridines are probably present as the keto forms in aqueous solution, whereas the 8-hydroxy-1,6-naphthyridine occurs as such.

⁵⁰ N. P. Buü-Hoi, P. Jacquignon, O. Roussel-Périn, F. Perin, and M. Mangane, *J. Heterocyclic Chem.* **4**, 415 (1967).

⁵¹ F. Haglid, *Acta Chem. Scand.* **21**, 580 (1967).

⁵² A. Albert and J. Philips, *J. Chem. Soc.* 1294 (1956).

⁵³ K. Allen, J. Cymerman-Craig, and A. Diamantis, *J. Chem. Soc.* 234 (1954).

⁵⁴ A. Albert and A. Hampton, *J. Chem. Soc.* 505 (1954).

⁵⁵ A. Albert and W. L. F. Armarego, *J. Chem. Soc.* 4237 (1963).

⁵⁶ W. W. Paudler and T. J. Kress, *J. Heterocyclic Chem.* **5**, 561 (1968).

TABLE VI
IONIZATION CONSTANTS OF SOME NAPHTHYRIDINES

Compound	$pK_a^{a,b}$	Ref.
1,5-Naphthyridine	2.91	11, 52
1,6-Naphthyridine	3.78	11
1,7-Naphthyridine	3.63	11
1,8-Naphthyridine	3.39	11
2,4-Dimethyl-7-amino-1,8-naphthyridine	6.67 ^c	53
4-Hydroxy-1,5-naphthyridine	2.85	52, 54
8-Hydroxy-1,6-naphthyridine	4.08	54
8-Hydroxy-1,7-naphthyridine	2.64	54
8-Hydroxy-1,6-naphthyridine 6-methiodide	4.34	54
<i>trans</i> -Decahydro-1,5-naphthyridine	10.16 (6.86)	44
<i>cis</i> -Decahydro-1,5-naphthyridine	10.31 (6.65)	44
<i>trans</i> -Decahydro-1,6-naphthyridine	10.68 (8.18)	44
<i>trans</i> -Decahydro-1,7-naphthyridine	10.16 (7.07)	44
<i>trans</i> -Decahydro-1,8-naphthyridine	9.36 (4.82)	44
1,2,3,4-Tetrahydro-1,5-naphthyridine	6.96 (−1.35) ^d	44
1,2,3,4-Tetrahydro-1,6-naphthyridine	10.19 ^d	44
1,2,3,4-Tetrahydro-1,7-naphthyridine	7.08 (−1.35) ^d	44
5,6,7,8-Tetrahydro-1,7-naphthyridine	8.56 (2.48) ^d	44
1,2,3,4-Tetrahydro-1,8-naphthyridine	7.61 ^d	44
3-Nitro-1,6-naphthyridine	2.32 ^d	55
8-Nitro-1,6-naphthyridine	2.59 ^d	55
3-Nitro-1,5-naphthyridine	0.63 ^d	55

^a Determined potentiometrically, at 20°, in water, unless otherwise stated.

^b Values in parentheses are for the addition of a second proton.

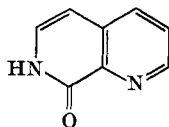
^c In 50% aqueous ethanol.

^d Determined spectrophotometrically.

The base-strengthening effect of an 8-hydroxy group in 1,6-naphthyridine is attributable to hydrogen bonding of the hydroxyl group with the N-1 nitrogen atom, which enhances the electron-donor properties of the hydroxyl. As Albert suggests, N-6 is protonated in both 1,6-naphthyridine and its 8-hydroxy derivative.⁵⁴ The complex-forming ability of some 8-hydroxy-1,*x*-naphthyridines with metal ions has been investigated and correlated with their ionizing properties and their bactericidal action.^{54, 57}

⁵⁷ A. Albert and A. Hampton, *Spec. Lectures Biochem. Univ. Coll. London* p. 96 (1954); *Chem. Abstr.* **52**, 8281 (1958).

A noteworthy feature is the considerable base-weakening effect that an 8-hydroxy group has on the pK_a of 1,7-naphthyridine ($\Delta pK_a = 1.0$). We would expect the pK_a of 8-hydroxy-1,7-naphthyridine (**16**) to be similar to that of the 4-hydroxy-1,5-isomer (**15**) since similar electronic factors are operative in these two compounds. This is



(16)

indeed the case. The somewhat lower pK_a of the 1,7-compound (2.64) as compared to the 1,5-isomer (2.85) is also to be expected.

Among the nitronaphthyridines whose pK_a 's have been reported,⁵⁸ the pK_a of 3-nitro-1,5-naphthyridine appears, at first glance, exceedingly low (0.63). If one considers the resonance contributing structures possible for the 1,5-isomer, it becomes clear, however, that in this instance the nitrogen atom in the ring not containing the nitro group is strongly depleted of its electrons by the resonance effect of the nitro group. This effect is *not* operative in the 3-nitro-1,6- and the 8-nitro-1,6-isomers, where the nitro groups deactivate only by their inductive electron withdrawal effect.

III. Syntheses

A. PREPARATION OF 1,5-NAPHTHYRIDINES

1. The Skraup Reaction

The unsubstituted compound, 1,5-naphthyridine, can easily be prepared by application of the Skraup reaction to 3-aminopyridine. This reaction has been modified several times,^{17, 59, 60} and a yield of 60–70% may now be realized. Rapoport and Batcho¹⁶ have shown that cyclization takes place exclusively at the 2-position of the 3-aminopyridine in the Skraup reaction since none of the isomeric 1,7-naphthyridine is formed in the absence of a blocking group at that site.

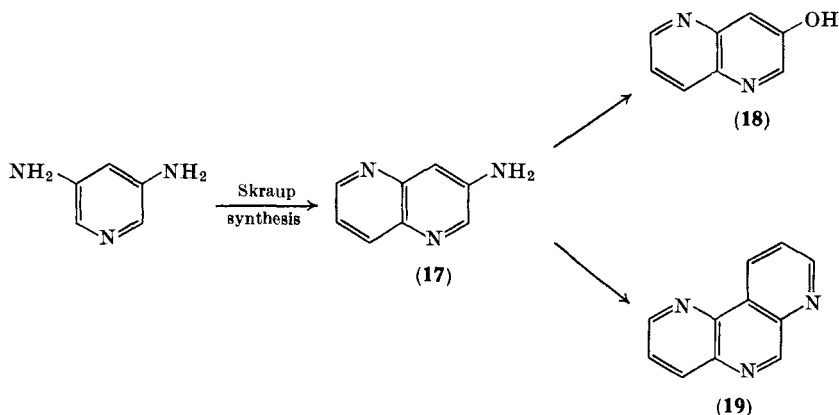
⁵⁸ A. Albert and W. L. F. Armarego, *J. Chem. Soc.* 4237 (1963).

⁵⁹ C. R. Hauser and G. Reynolds, *J. Org. Chem.* **15**, 1224 (1950).

⁶⁰ E. P. Hart, *J. Chem. Soc.* 1879 (1954).

When the blocking group is other than a halogen atom or a keto group, only tars are formed. 8-Hydroxy-1,7-naphthyridine⁶¹ is obtained from 3-amino-2-hydroxypyridine, and 1,5-naphthyridine is obtained from the 2-halo-3-aminopyridines when they are subjected to the Skraup reaction. 3-Aminopyridine 1-oxide affords the parent 1,5-naphthyridine,⁶² and both 3-amino-6-hydroxypyridine and 3-amino-6-chloropyridine give 2-hydroxy-1,5-naphthyridine.⁶³ Hart⁶⁴ has applied the Skraup synthesis to 3-amino-4-hydroxypyridine and has obtained the expected 4-hydroxy-1,5-naphthyridine.

Czuba⁶⁵ has reported the isolation of three products (**17**–**19**) from the Skraup reaction with 3,5-diaminopyridine and has suggested that the 3-amino-1,5-naphthyridine is the logical precursor to compounds **18** and **19**.



2,5-Diaminopyridine, on the other hand, afforded 2-amino-1,5-naphthyridine^{66, 67} as the sole isolated product.

3-Aminoquinoline has been reported⁶⁸ to give the linear benzo-1,5-naphthyridine (**20**), Buü-Hoi and co-workers⁶⁹ have contested this

⁶¹ A. Albert and A. Hampton, *J. Chem. Soc.* 4985 (1952).

⁶² J. G. Murray and C. R. Hauser, *J. Org. Chem.* **19**, 2008 (1954).

⁶³ C. Roth, German Patent 507,637 (1926); *Chem. Abstr.* **25**, 716 (1931).

⁶⁴ E. P. Hart, *J. Chem. Soc.* 212 (1956).

⁶⁵ W. Czuba, *Roczniki Chem.* **41**, 289 (1967).

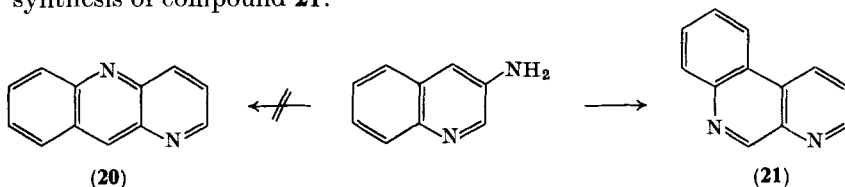
⁶⁶ K. Miyaki, *J. Pharm. Soc. Japan* **62**, 257 (1942); *Chem. Abstr.* **45**, 2950 (1951).

⁶⁷ W. Czuba, *Rec. Trav. Chim.* **82**, 988 (1963).

⁶⁸ M. Shimizu, *J. Pharm. Soc. Japan* **64**, 489 (1944).

⁶⁹ N. P. Buü-Hoi, R. Royer, and M. Hubert-Habart, *J. Chem. Soc.* 2048 (1956).

conclusion and suggested the benzo-1,7-naphthyridine structure (21) on the basis of the UV similarity with some azaphenanthrenes. More recently,⁴⁵ the latter conclusion has been confirmed by nuclear magnetic resonance (NMR) spectral data and by an unequivocal synthesis of compound 21.



The condensing agents used in the Skraup and related reactions are not limited to glycerol. Table VII lists some of the carbonyl compounds and aminopyridines which have been successfully used to prepare various 1,5-naphthyridines. The majority of the dimethyl- and trimethyl-1,5-naphthyridines still remain unknown simply because of the difficulties involved in the preparation of the various 3-aminopicolines and 3-aminolutidines.

TABLE VII
PREPARATIVE DATA OF SOME 1,5-NAPHTHYRIDINES

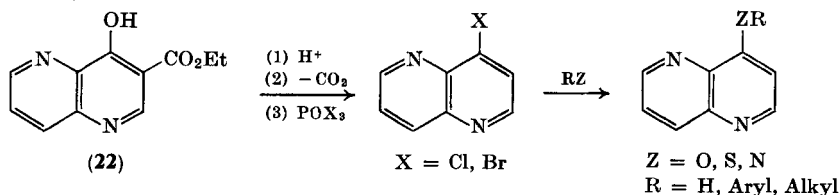
Substituents in 3-aminopyridine	Condensing reagent	Substituents in product	Ref.
None	Glycerol	None	16
None	Crotonaldehyde	2-Methyl	16
None	Methacrolein	3-Methyl	16
None	Methyl vinyl ketone	4-Methyl	16
None	2-Ethylacrolein	3-Ethyl	16
None	Acetaldehyde and acetone	2,4-Dimethyl	66
4-Hydroxy	Glycerol	4-Hydroxy	64
6-Hydroxy	Glycerol	6-Hydroxy	63, 70
6-Hydroxy	Acetaldehyde	6-Hydroxy-2-methyl	70
6-Hydroxy	Acetaldehyde and acetone	6-Hydroxy-2,4-dimethyl	66
6-Chloro	Acetaldehyde	6-Chloro-2-methyl	71
1-Methyl-5-aminopyrid-2-one	Acetaldehyde	1,6-Dimethyl-1,5-naphthyridin-2-one	70

⁷⁰ V. Petrow and B. Sturgeon, *J. Chem. Soc.* 1157 (1949).

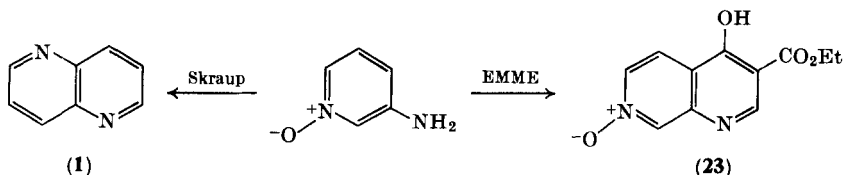
⁷¹ T. Takahashi, T. Yatsuka, and S. Senda, *J. Pharm. Soc. Japan* **64**, 9 (1944); *Chem. Abstr.* **46**, 110 (1952).

2. *EMME Syntheses*

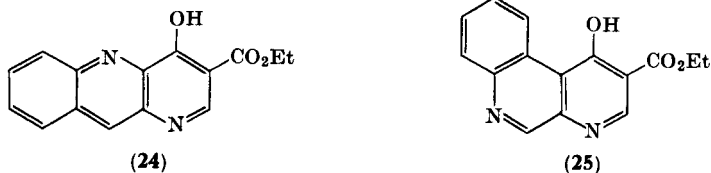
Another general procedure^{72, 73} for the preparation of 1,5-naphthyridines requires the heating of the condensation product of 3-aminopyridine or a substituted 3-aminopyridine and diethyl ethoxymethylenemalonate (EMME) in refluxing "Dowtherm A" to afford 3-carbethoxy-4-hydroxy-1,5-naphthyridine (**22**). This reaction allows the introduction of various groups into the 3- and the 4-positions, as illustrated.



It is of interest that, although the Skraup reaction⁶² on 3-aminopyridine 1-oxide affords 1,5-naphthyridine, the EMME synthesis on this compound affords the 1,7-naphthyridine-7-oxide.²³ It has been suggested that the 3-aminopyridine 1-oxide is deoxygenated prior to the Skraup reaction so that, in fact, it is 3-aminopyridine that is directly converted to the 1,5-naphthyridine. The EMME cyclization, on the other hand, follows the expected direction of cyclization.



The EMME synthesis with 3-aminoquinoline was incorrectly described as yielding the linear compound **24**. Later workers^{45, 74} showed that the product was the angular benzo-1,7-naphthyridine (**25**).



⁷² J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore, and C. R. Hauser, *J. Am. Chem. Soc.* **68**, 1317 (1946).

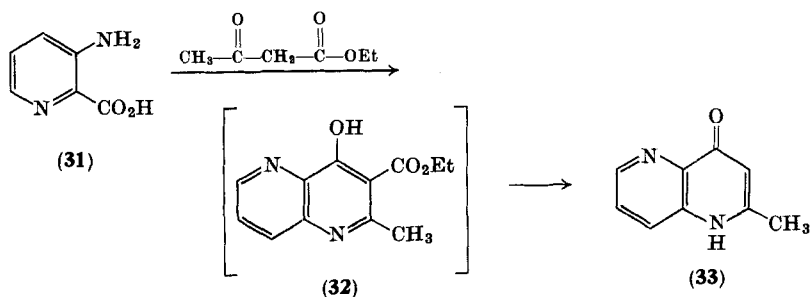
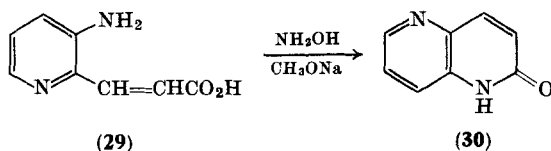
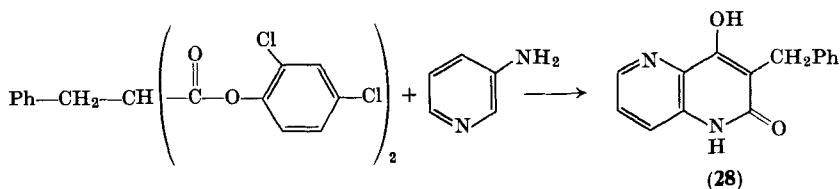
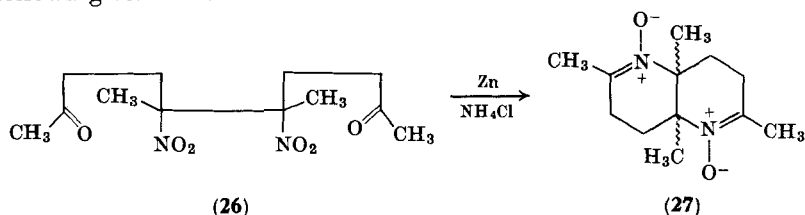
⁷³ C. C. Price and R. M. Roberts, *J. Am. Chem. Soc.* **68**, 1204 (1946).

⁷⁴ G. Leshner, U.S. Patent 3,300,499 (1967); *Chem. Abstr.* **66**, 95020 (1967).

3. Miscellaneous Preparations

A novel synthesis⁷⁵ of, presumably, a hexahydro-1,5-naphthyridine (27) resulted as a by-product of the preparation of a dipyrrolyl derivative by reductive cyclization of the ketone 26. The stereochemistry about the bridgehead carbon atoms was not established.

Ziegler and Noelken⁷⁶ prepared the 1,5-naphthyridinone 28 by the following condensation.



⁷⁵ R. F. C. Brown, V. M. Clark, M. Lamchen, and A. Todd, *J. Chem. Soc.* 2116 (1959).

⁷⁶ E. Ziegler and E. Noelken, *Monatsh. Chem.* **92**, 1184 (1961).

The 2,3-disubstituted pyridines (**29** and **31**) were converted into 2-hydroxy- (**30**) and 2-methyl-4-hydroxy-1,5-naphthyridine (**33**), respectively,⁷⁷ by the following sequences.

The intermediate **32** underwent hydrolysis and decarboxylation under the reaction conditions.

B. PREPARATION OF 1,6-NAPHTHYRIDINES

The obvious method for the preparation of this naphthyridine is the Skraup reaction applied to 4-aminopyridine; after early failures,⁶ ⁸⁰ the authors of this chapter⁸¹ utilized the "sulfo-mix" described by Utermohlen,⁸² to obtain 1,6-naphthyridine (**2**) in 40% yield.

Several other syntheses^{8, 11, 78, 79} have been described, but all these involve at least seven-step sequences, with typical overall yields of less than 2%.

Kato and co-workers⁸³ have applied the Skraup reaction to 4-aminopyridine 1-oxide and some of its methyl derivatives and have obtained the parent 6-oxide, the 5,7-dimethyl-, 5-methyl-, 7-methyl-, and the 8-methyl-1,6-naphthyridine 6-oxides. 1,6-Naphthyridine 6-oxide has also been prepared from 4-aminopyridine *N*-oxide and 1,1-diacetoxy-2-propene.⁸⁴

The *N*-oxides were used as the starting material on the assumption that the free amines would not undergo the cyclization reaction. This assumption is now, of course, no longer tenable. The reported yields of the naphthyridine *N*-oxides were, unfortunately, less than 5%.

As in the case of the 1,5-naphthyridines, the Skraup reaction can be modified to prepare various methyl derivatives. The use of crotonaldehyde, methacrolein, and methyl vinyl ketone affords the 2-methyl-,⁴⁰ 3-methyl-,⁴¹ and 4-methyl-1,6-naphthyridines,⁴⁰ respectively.

⁷⁷ H. E. Baumgarten, H. C. F. Su, and R. P. Barkley, *J. Heterocyclic Chem.* **3**, 357 (1966).

⁷⁸ B. M. Ferrier and N. Campbell, *Proc. Roy. Soc. Edinburgh* **A65**, 23 (1959-1960); *Chem. Abstr.* **55**, 24748 (1961).

⁷⁹ L. Weintraub, Ph.D. Thesis, New York University, New York (1954).

⁸⁰ B. Bobranski and E. Sucharda, *Roczniki Chem.* **7**, 192 (1927).

⁸¹ T. J. Kress and W. W. Paudler, *Chem. Commun.* **3** (1967).

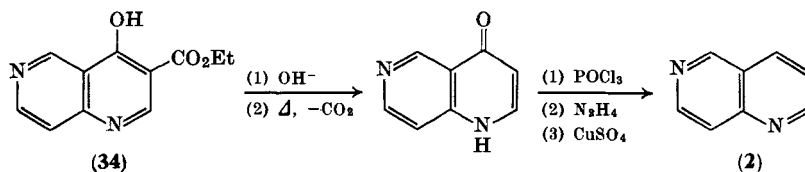
⁸² W. P. Utermohlen, Jr., *J. Org. Chem.* **8**, 544 (1943).

⁸³ T. Kato, F. Hamaguchi, and T. Oiwa, *Chem. Pharm. Bull. (Tokyo)* **4**, 178 (1956).

⁸⁴ S. Tamura, T. Kudo, and Y. Yanagishara, *Yakugaku Zasshi* **80**, 562 (1960); *Chem. Abstr.* **54**, 22650 (1960).

1. *EMME Syntheses*

The condensation and cyclization of EMME with 4-aminopyridine and 4-aminoquinoline affords, in each case, the 1,6-naphthyridine ring system.⁵⁹ Albert¹¹ used this reaction to prepare the hydroxy ester (34), which he converted into the parent 1,6-naphthyridine by the following sequence of reactions.



This scheme has been used by several other groups of workers and the overall yield of the parent naphthyridine has been substantially improved.^{39, 85}

Okuda condensed 4-amino-2,6-lutidine with EMME and converted the resulting hydroxy ester into 5,7-dimethyl-1,6-naphthyridine.⁸⁶

Although other condensation reactions with 4-aminopyridine are reported to fail, they have in most cases succeeded with 4-aminoquinoline.⁵⁹ Dey and Joullié⁸⁷ have prepared a series of trifluoromethylbenzo[*h*]-1,6-naphthyridines by condensing ethyl trifluoromethylacetate with 4-aminoquinoline.

2. *Miscellaneous Syntheses*

The base-catalyzed rearrangement of the cyclic imide (35) affords a 50% yield of the 1,6-naphthyridine (36) and a 20% yield of the isomeric 1,7-naphthyridine (37).⁶¹ Treatment of 38, obtained by hydrolysis and decarboxylation of 36, with phosphorus oxychloride is reported to give 5-chloro-8-hydroxy-1,6-naphthyridine (39).⁸⁸

The structure of the product obtained by condensing acetone, in the presence of hydrobromic acid, with the nitrile 40 is suggested to be the naphthyridine (41).⁸⁹ Structure confirmation would be desirable.

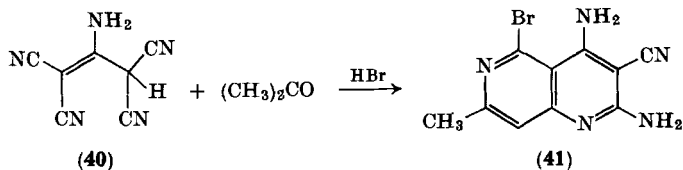
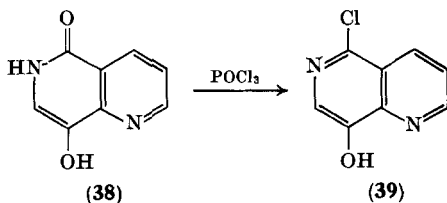
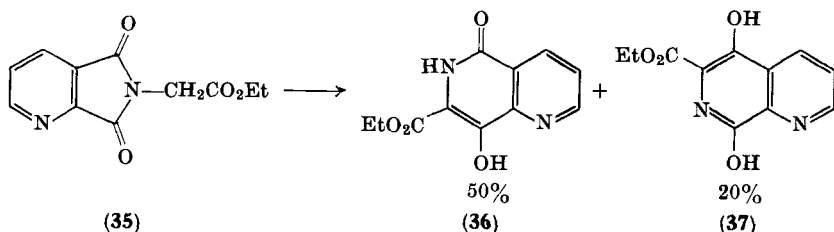
⁸⁵ K. Möller and O. Süss, *Ann. Chem.* **612**, 153 (1958).

⁸⁶ S. Okuda, *Chem. Pharm. Bull. (Tokyo)* **5**, 460 (1957).

⁸⁷ A. S. Dey and M. M. Joullié, *J. Heterocyclic Chem.* **2**, 120 (1965).

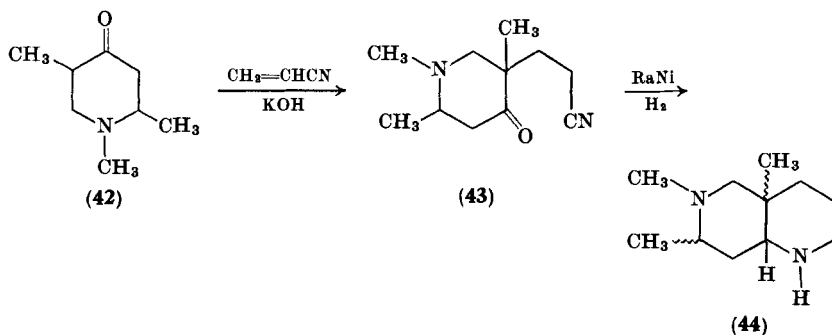
⁸⁸ E. Ochiai and K. Miyaki, *J. Pharm. Soc. Japan* **58**, 764 (1938); *Chem. Abstr.* **33**, 2525 (1939).

⁸⁹ E. L. Little, Jr., W. J. Middleton, D. D. Coffman, V. A. Enghardt, and G. N. Sausen, *J. Am. Chem. Soc.* **80**, 2832 (1958).



The piperidine derivative (42), on treatment with acrylonitrile in base, affords 43, which, on catalytic reduction, gives the perhydro-1,6-naphthyridine (44) of unspecified stereochemistry.⁹⁰

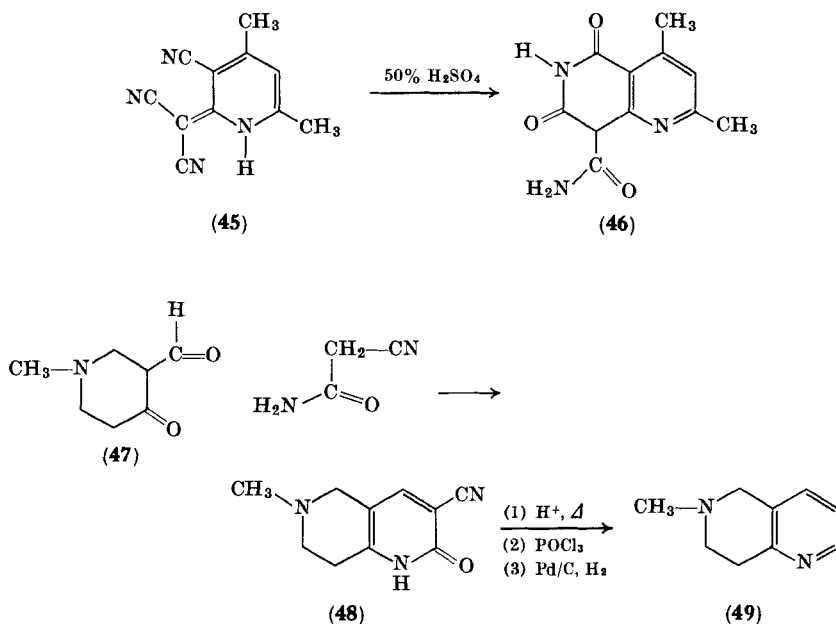
Treatment of 45 with acid is reported to yield the dimethylnaphthyridine 46.⁹¹



⁹⁰ I. N. Nazarov, G. A. Shvekhgheymer, and A. V. Rudenko, *Zh. Obshch. Khim.* **24**, 319 (1954); *Chem. Abstr.* **49**, 4651 (1955).

⁹¹ H. Junek, *Monatsh. Chem.* **96**, 2046 (1965).

Condensation of *N*-methyl-3-formyl-4-piperidone (**47**) with cyanoacetamide afforded the tetrahydro-1,6-naphthyridine (**48**). This compound was converted into the 5,6,7,8-tetrahydro-6-methyl-1,6-naphthyridine (**49**) by the transformations shown.⁹²



The discovery of the alkaloid halozine, which contains the 1,6-naphthyridine ring skeleton, has led to the syntheses of some perhydro derivatives. These transformations will be discussed in Section VI.

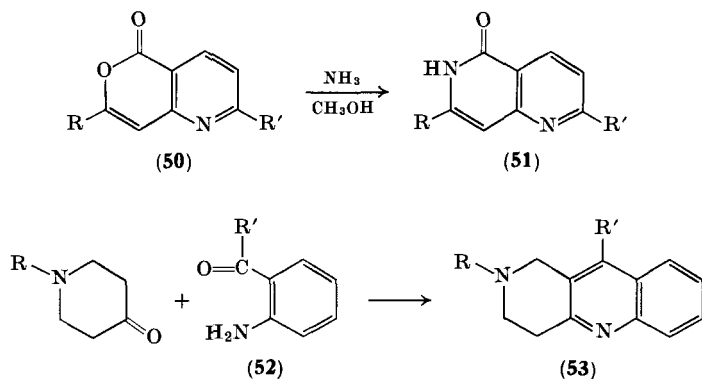
Treatment of the pyranopyridine (**50**) with methanolic ammonia gave compound **51**.⁹³ This is the same reaction used earlier by Ikekawa to form the 1,6-naphthyridine ring system.

Several benzonaphthyridines of type **53** have been prepared⁸¹ by condensing 4-piperidones with β -aminocarbonyl compounds such as **52**.⁹⁴

⁹² F. Haglid, *Arkiv. Kemi* **26**, 489 (1967); *Chem. Abstr.* **67**, 32611 (1967).

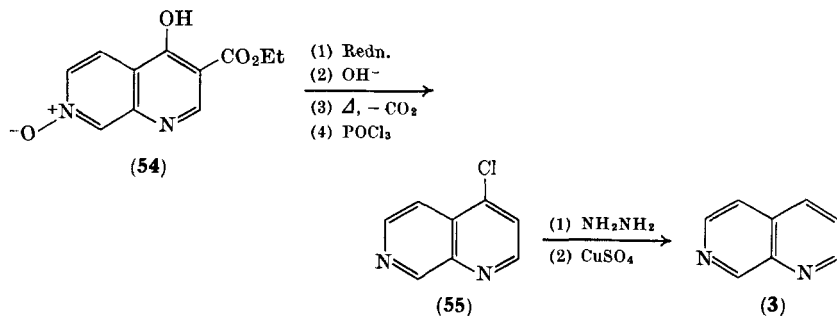
⁹³ D. G. Wibberley, *J. Chem. Soc.* 4529 (1962).

⁹⁴ G. Kempter and S. Hirschberg, *Z. Chem.* **4**, 29 (1964); *Chem. Abstr.* **60**, 8005 (1964).



C. PREPARATION OF 1,7-NAPHTHYRIDINES

Murray and Hauser⁶² reported that the cyclization of the condensation product of 3-aminopyridine *N*-oxide and EMME affords the 1,7-naphthyridine derivative (54). This compound was converted into the chloro derivative (55) by the steps outlined below. Both Ikekawa⁹ and Albert¹¹ converted compound 55 into the parent 1,7-naphthyridine (3) by oxidation of the hydrazino derivative. This synthetic route constituted the first preparation of the parent compound.



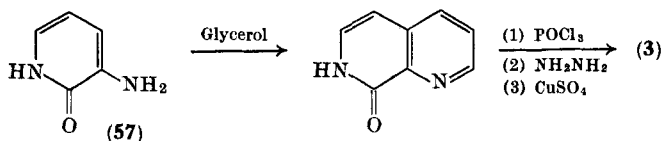
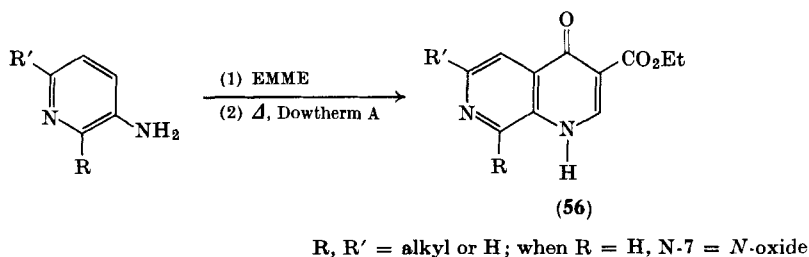
The wide applicability of the EMME condensation in the synthesis of 1,7-naphthyridines (56) has recently been demonstrated by chemists at the Sterling Drug Company.⁹⁵ This condensation occurs in the

⁹⁵ Sterling Drug Inc., British Patent 1,022,214 (1966); *Chem. Abstr.* **64**, 19618 (1966).

absence of the directing effect of the *N*-oxide group as long as there is a blocking group in the 2-position.

The similar condensation of 3-aminoquinoline with EMME to give benzo-1,7-naphthyridines has been described earlier (see Section III, A).

The Skraup reaction has, in general, had limited applicability to the synthesis of 1,7-naphthyridines, and has been successful in only a few isolated cases. The easiest synthesis of the parent 1,7-naphthyridine does, however, utilize the Skraup reaction. Since its original description, the synthesis has been improved,¹⁶ so that 1,7-naphthyridine



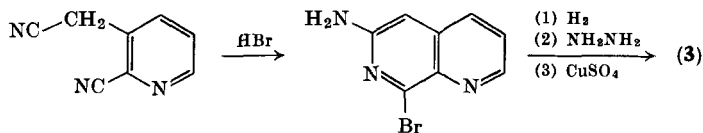
can now be obtained in four steps from 3-amino-2-pyridone (57). The Skraup reaction⁹⁶ with 2,3-diaminopyridine affords, 8-amino-1,7-naphthyridine.

Tan and Taurins¹⁸ recently reported a new synthesis of 1,7-naphthyridine (3) which involves a six-step sequence starting with ethyl 2-cyano-3-pyridyl acetate. Although the overall yield is low, the method is of value since it can be modified to yield 6- and 8-substituted derivatives. The later reactions in this sequence are outlined below.

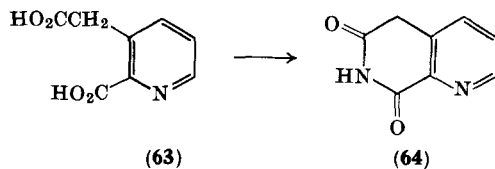
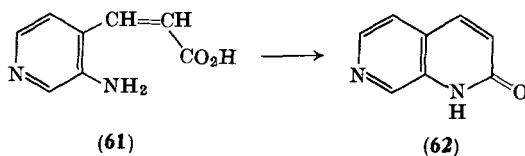
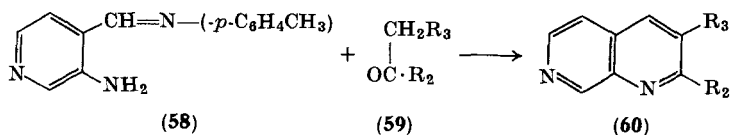
The Borsche modification of the Friedlander quinoline synthesis has been shown to be of general use⁹⁷ in the preparation of 1,7-naphthyridines (60). The preparative sequence involves the synthesis of compound 58 and its condensation with a carbonyl compound (59).

⁹⁶ W. W. Paudler and T. J. Kress, *J. Org. Chem.* **33**, 1384 (1968).

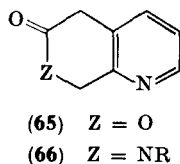
⁹⁷ H. E. Baumgarten and K. C. Cook, *J. Org. Chem.* **22**, 138 (1957).



Two other modifications of quinoline syntheses which afford 1,7-naphthyridinones (**62** and **64**) have been successful.⁹⁸ However, the starting materials, compounds **61** and **63** are not readily accessible.



The lactone (**65**) with a variety of primary amines afforded various tetrahydro-1,7-naphthyridines (**66**).⁹⁹

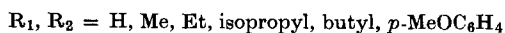
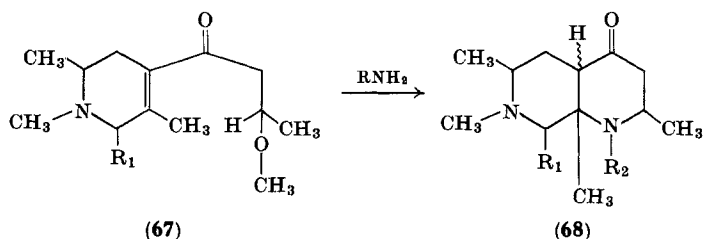


A wide variety of 1-*N*-alkylperhydro-1,7-naphthyridines (**68**) were prepared¹⁰⁰ by reacting the ether (**67**) with various alkyl amines.

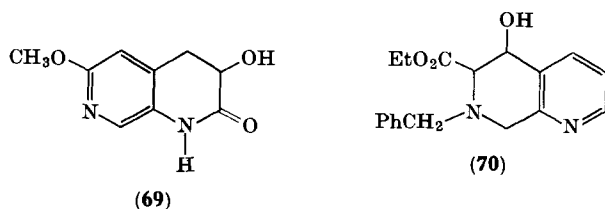
⁹⁸ H. E. Baumgarten and A. L. Krieger, *J. Am. Chem. Soc.* **77**, 2438 (1955).

⁹⁹ Y. Sato, T. Iwashige, and T. Miyadera, Japanese Patent 4149 (1962); *Chem. Abstr.* **59**, 2823 (1963).

¹⁰⁰ B. Frydman, M. E. Despuuy, and H. Rapoport, *J. Am. Chem. Soc.* **87**, 3530 (1965).



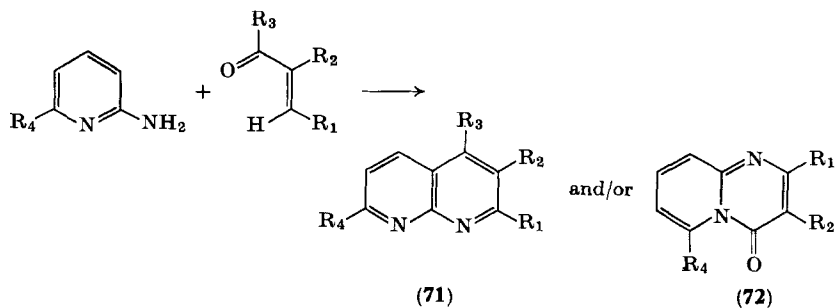
Two additional tetrahydro derivatives (69 and 70) have been prepared¹⁰¹ by exocyclic ester condensations of substituted pyridines.



The preparation of 1,7-naphthyridines by ring expansion of cyclic imides has previously been discussed (see Section III, A).

D. PREPARATION OF 1,8-NAPHTHYRIDINES

The logical starting material for the preparation of 1,8-naphthyridines is a 2-aminopyridine. Although frequently used, such cyclizations are complicated by competing reactions at the 3-position of the pyridine ring to give the naphthyridine (71), and at the ring nitrogen to form pyrido[1,2-*a*]pyrimidines (72).



¹⁰¹ F. Zymalkowski and P. Messinger, *Arch. Pharm.* **300**, 91 (1967); *Chem. Abstr.* **67**, 43695 (1967).

The condensation of 2-aminopyridine with EMME followed by cyclization in Dowtherm affords the pyridopyrimidine (**72**).^{102, 103} When the 2-aminopyridine is substituted in the 6-position with an electron-releasing group ($R_4 = \text{CH}_3, \text{OEt}, \text{NH}_2$), the naphthyridine (**71**) is formed.⁷² In all cases of the EMME reaction and condensations involving similar carbonyl compounds, that have been studied, the naphthyridine is formed only when this latter requirement is fulfilled.

The synthesis of 1,8-naphthyridines using adaptations of quinoline syntheses (Knorr, Conrad-Limpach, Combs, Chichibabin, Doebner, and Doebner-Miller) has been discussed by Hauser and Weiss¹⁰⁴ and the reader is referred to this work for details.

TABLE VIII
PREPARATIVE DATA OF SOME 1,8-NAPHTHYRIDINES

Substituents in 2-aminopyridine	Condensing reagent	Substituents in product	Yield (%)	Melting point (°C)	Ref.
None	Glycerol	None	30	98–99	46
4-Methyl	Glycerol	4-Methyl	17	204–205 ^a	46
4-Methyl	Crotonaldehyde	2,5-Dimethyl	17	85–87	41
4-Methyl	Methyl vinyl ketone	4,5-Dimethyl	3	152–153.5	41
5-Methyl	Glycerol	3-Methyl	18	119–120	41
5-Methyl	Crotonaldehyde	2,6-Dimethyl	1.5	161–163	41
5-Methyl	Methyl vinyl ketone	3,5-Dimethyl	3	86–87	41
5-Methyl	Methacrolein	3,6-Dimethyl	1	192–193	41
6-Methyl	Glycerol	2-Methyl	10	99–100	46
6-Methyl	Crotonaldehyde	2,7-Dimethyl	15	194–195	41
4,6-Dimethyl	Glycerol	2,4-Dimethyl	10	84–85	46
4,6-Dimethyl	Crotonaldehyde	2,4,7-Trimethyl	16	98.5–99.5	41

^a Picrate.

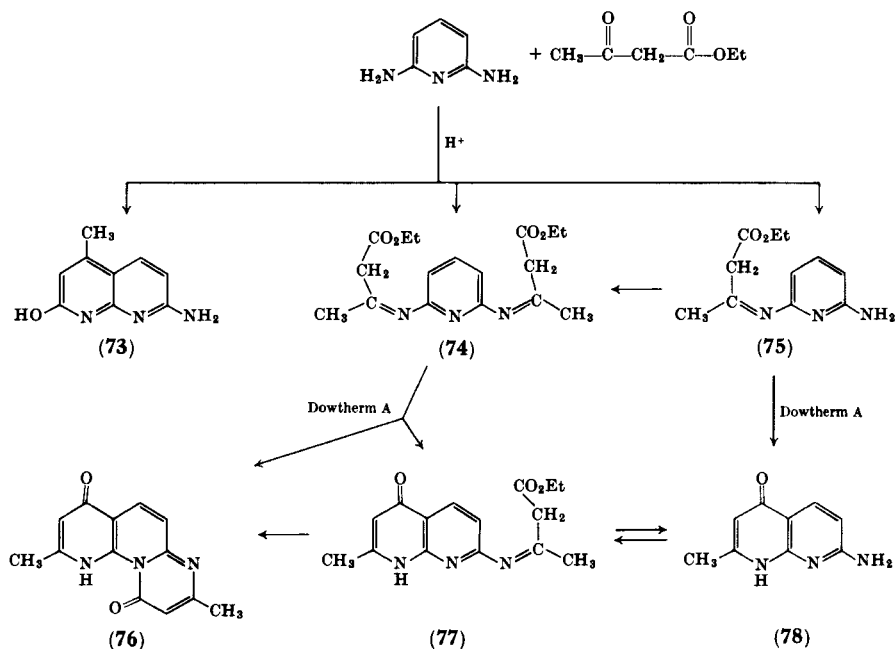
As with 4-aminopyridine, the Skraup reaction on 2-aminopyridine was reported to have failed; the authors have shown that the transformation to a 1,8-naphthyridine is, in fact, facile.^{41, 46} Since 1,5-naphthyridine and 1,6-naphthyridine are isolated from the reaction mixtures by steam distillation, while 1,8-naphthyridine

¹⁰² R. Adams and I. J. Pachter, *J. Am. Chem. Soc.* **74**, 5491 (1952).

¹⁰³ G. R. Lappin, *J. Am. Chem. Soc.* **70**, 3348 (1948).

¹⁰⁴ C. R. Hauser and M. J. Weiss, *J. Org. Chem.* **14**, 453 (1949).

is not steam-volatile. It is probable that earlier reported failures of the Skraup reaction with 2-aminopyridines may be accounted for by the attempted use of the traditional steam distillation isolation procedures. By the condensation of 2-aminopyridines, picolines, and lutidines with glycerol, crotonaldehyde, 2-methylacrolein, or methyl vinyl ketone all the mono-, di-, and trimethyl-1,8-naphthyridines are now available. Thus far, all the monomethyl-, seven of the nine possible dimethyl-, and one trimethyl-1,8-naphthyridine have been prepared by the modified Skraup procedure (see Table VIII). The 2,3-dimethyl-, the 3,4-dimethyl-, and all the trimethyl-1,8-naphthyridines except the 2,4,7-derivative remain unknown.



SCHEME 1

E. V. Brown¹⁰⁵ has described the synthesis of 2-methyl-1,8-naphthyridine, and several new derivatives by the EMME synthesis, starting with 2-amino-6-methylpyridine.

The condensation of 2,6-diaminopyridine with ethyl acetoacetate under Conrad-Limpach conditions is reported to give 2-methyl-4-

¹⁰⁵ E. V. Brown, *J. Org. Chem.* **30**, 1607 (1965).

hydroxy-7-amino-1,8-naphthyridine¹⁰⁴ as well as the dianil (**74**). It has been demonstrated by two groups of workers,^{105, 106} however, that the naphthyridine formed is the 2-hydroxy-4-methyl-7-amino-1,8-naphthyridine (**73**). Carboni and co-workers¹⁰⁷ have since studied this reaction in great detail and have obtained some interesting results (Scheme 1).

Compound **73** corresponds to the "Knorr-type" product, whereas compounds **74** and **75** are the intermediate anils expected in a Conrad-Limpach-type condensation. Thermal cyclization of compounds

TABLE IX

SOME 1,8-NAPHTHYRIDINES FROM 2,6-DIAMINOPYRIDINE

Carbonyl compound	Substituents in product at positions				Ref.
	2	3	4	7	
Ethyl 2-oxalylpropionate	OH	CH ₃	COOH	NH ₂	108
Ethyl oxalacetate	OH	COOEt	—	NH ₂	109
Malic acid	OH	—	—	NH ₂	110
Ethyl β -methylmalate	OH	CH ₃	—	NH ₂	110
Citric acid	OH	—	CH ₂ COOH	NH ₂	110
Acetonedicarboxylic acid	OH	—	CH ₂ COOH	NH ₂	110
Ethyl oxalate	OH	—	COOH	NH ₂	114

¹⁰⁶ S. Carboni, A. DaSettimo, and G. Pirisino, *Ann. Chim. (Rome)* **54**, 667 (1964); *Chem. Abstr.* **61**, 11980 (1964).

¹⁰⁷ S. Carboni, A. DaSettimo, G. Pirisino, and D. Segnini, *Gazz. Chim. Ital.* **96**, 103 (1966).

¹⁰⁸ S. Carboni and P. Geralamo, *Ann. Chim. (Rome)* **52**, 340 (1962); *Chem. Abstr.* **57**, 9825 (1962).

¹⁰⁹ S. Carboni and G. Pirisino, *Ann. Chem. (Rome)* **52**, 279 (1962); *Chem. Abstr.* **57**, 279 (1962).

¹¹⁰ S. Carboni, A. DaSettimo, and G. Pirisino, *Ann. Chim. (Rome)* **54**, 883 (1964); *Chem. Abstr.* **63**, 5620 (1965).

¹¹¹ S. Carboni, A. DaSettimo, D. Segnini, and I. Tonetti, *Gazz. Chim. Ital.* **96**, 1443 (1966).

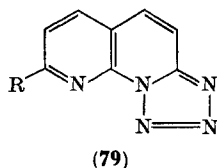
¹¹² S. Carboni, A. DaSettimo and P. L. Ferrarini, *Gazz. Chim. Ital.* **97**, 1061 (1967).

¹¹³ S. Carboni, A. DaSettimo, P. L. Ferrarini, and G. Pirisino, *Gazz. Chim. Ital.* **96**, 1456 (1966); *Chem. Abstr.* **67**, 100084 (1967).

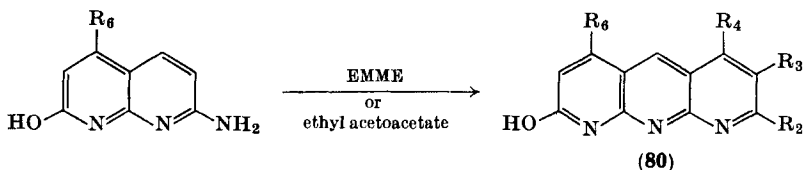
¹¹⁴ H. Suter and W. Kuendig, German Patent 829,894 (1954); *Chem. Abstr.* **52**, 1127 (1958).

74 and **75** in refluxing Dowtherm affords compounds **76–78**, respectively. Both products (**76** and **77**) can be converted into the naphthyridine (**78**) by base hydrolysis.

For other condensations with 2,6-diaminopyridine see Carboni *et al.*^{106–113} and Table IX. Several of these compounds have been converted into tetrazole derivatives (**79**) of 1,8-naphthyridine.¹¹¹



Some substituted 2-amino-1,8-naphthyridines have also been condensed with both EMME and ethylacetoacetate to give derivatives of a new ring system (**80**), described as “anthyrindines.”^{115, 116}



Several syntheses of 1,8-naphthyridines (**82**) from pyridines (**81**) already bearing substituents in the 2- and 3-positions have been reported.^{47, 48} These preparations are, however, limited in that the starting pyridine derivatives require multistep syntheses.

One route to the tetrahydro-1,8-naphthyridine (**84**) employs an intramolecular amination of compound **83** in the presence of sodium.⁴⁷

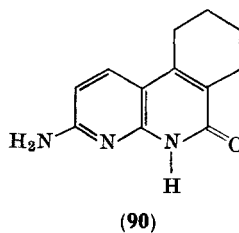
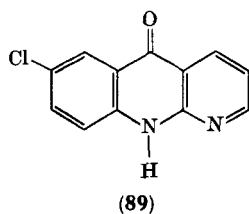
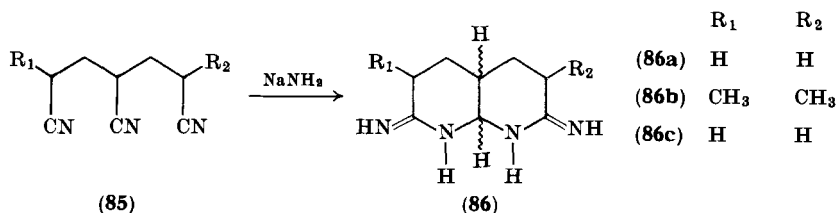
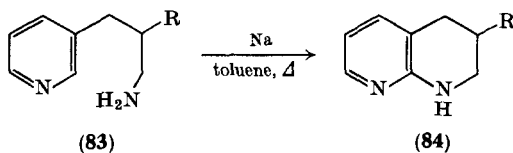
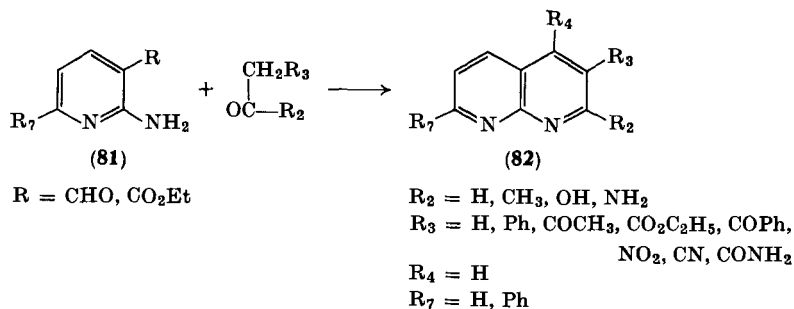
A novel cyclization reaction involving the heating of a 1,3,5-tricyanopentane (**85**) with sodium amide afforded the perhydro-1,8-naphthyridines (**86**).^{117, 118} The naphthyridine (**86b**) was converted into 3,6-dimethyl-1,8-naphthyridine in several steps.

¹¹⁵ S. Carboni, A. DaSettimo, P. L. Ferrarini, I. Tonetti, and D. Bertin, *Gazz. Chim. Ital.* **97**, 1274 (1967).

¹¹⁶ S. Carboni, A. DaSettimo, P. L. Ferrarini, I. Tonetti, and D. Bertin, *Gazz. Chim. Ital.* **97**, 1262 (1967).

¹¹⁷ T. Takata, *Bull. Chem. Soc. Japan* **35**, 1438 (1962); *Chem. Abstr.* **58**, 2451 (1963).

¹¹⁸ T. Takata and T. Okauchi, Japanese Patent 19,176 (1964); *Chem. Abstr.* **62**, 13151 (1965).



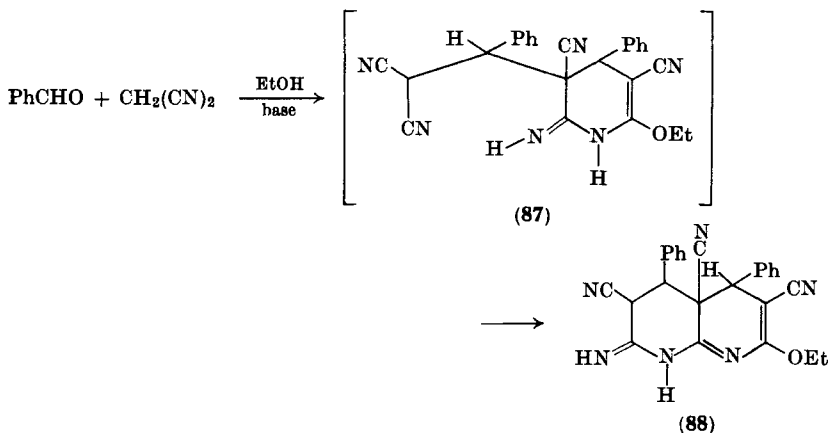
Malononitrile with benzaldehyde and ethanol in the presence of base is reported¹¹⁹ to give the naphthyridine (88), with derivative 87 suggested as an intermediate.

The two benzo-1,8-naphthyridines (89 and 90) have been prepared by treatment of *N*-(*p*-chlorophenyl)-2-aminonicotinic acid and *N,N'*-bis(2-oxohexahydrobenzoyl)-2,6-diaminopyridine, respectively, with sulfuric acid.^{120, 121}

¹¹⁹ M. R. S. Weir and J. B. Hyne, *Can. J. Chem.* **43**, 772 (1965).

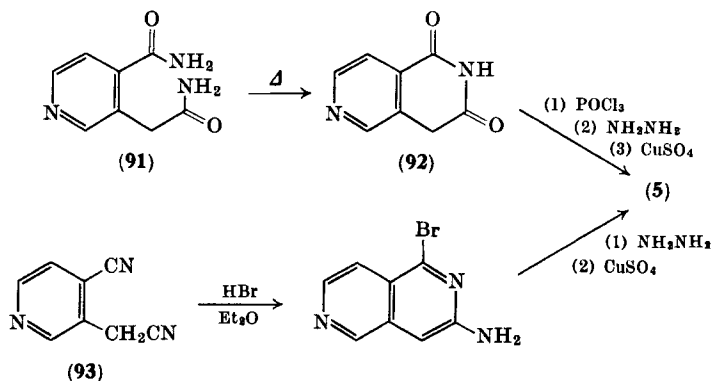
¹²⁰ P. Nantka-Namirski, *Acta Polon. Pharm.* **24**, 111 (1967); *Chem. Abstr.* **67**, 108538 (1967).

¹²¹ W. Ried and W. Kaeppler, *Ann. Chem.* **688**, 177 (1965).



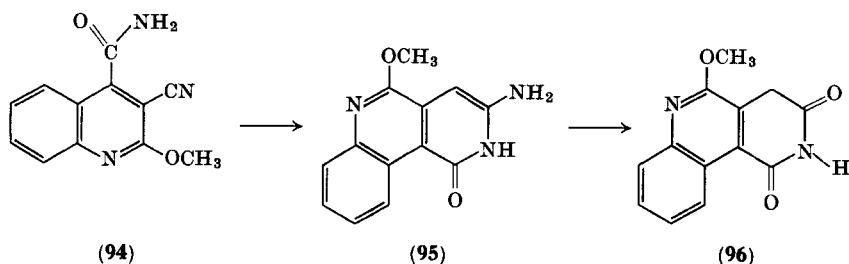
E. PREPARATION OF 2,6-NAPHTHYRIDINE

The parent 2,6-naphthyridine (**5**) has only recently been prepared and fewer publications concern this isomer than any of the other naphthyridines. Giacomello and co-workers¹² first synthesized the parent compound by a long sequence in which a key intermediate (**91**) was thermally cyclized. Compound **92** was converted into **5** by the conventional steps outlined below. Shortly afterwards, Tan and Taurins¹³ reported a synthesis starting from compound **93**.



The benzo[*b*]2,6-naphthyridine derivative (**95**) prepared from compound **94** has been converted into the benzo-2,6-naphthyridine-trione (**96**).¹²² Aside from a few derivatives of this isomer, prepared in

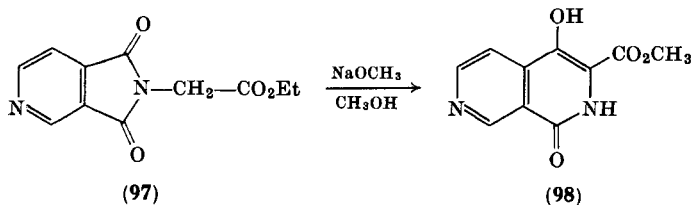
¹²² W. Ried and F. Kohlhaas, *Ann. Chem.* **707**, 242 (1967).



work on the alkaloid calycanthine (see Section VI), the above represents the extent of the literature on this ring system.

F. PREPARATION OF 2,7-NAPHTHYRIDINE

Similar to the ring enlargement of a cyclic imide to give 1,6- and 1,7-naphthyridines (see Section III, B) the imide **97** is reported¹²³ to undergo ring enlargement to form the hydroxy ester (**98**).

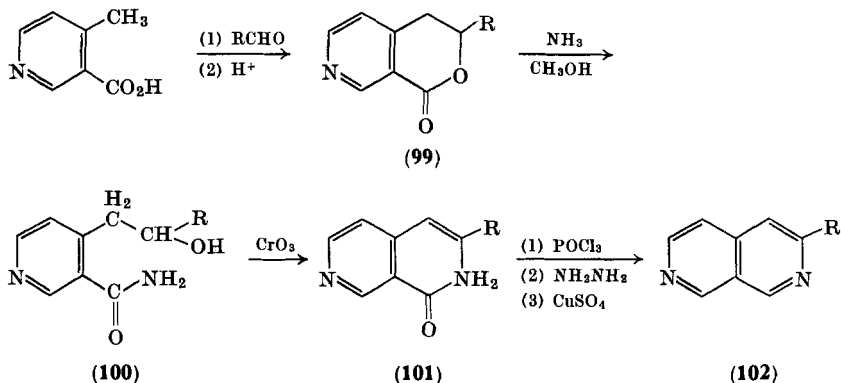


In 1958, Ikekawa¹⁰ synthesized 2,7-naphthyridine and various substituted derivatives. His approach involved the reaction of 4-methylnicotinic acid with formaldehyde to afford the lactone **99** ($R = H$). The reaction of **99** with ammonia in methanol yields the amide (**100**) which, on oxidation with chromium trioxide, afforded 2,7-naphthyridin-1-one (**101**). This substance was converted into 2,7-naphthyridine (**102**, $R = H$) by consecutive treatment with phosphorus oxychloride, hydrazine, and copper sulfate. The 3-methyl derivative was similarly prepared starting with acetaldehyde.

The reaction of nicotinamide methochloride (**103**) with acetone in the presence of base gives a fluorescent compound which Huff¹²⁴ assumed to be the hydrochloride of 1,7-dimethyl-5-oxo-1,6-naphthyridine (**104**). Based on this structure assignment, Birkofer and

¹²³ S. Gabriel and J. Colman, *Chem. Ber.* **35**, 1358 (1902).

¹²⁴ J. W. Huff, *J. Biol. Chem.* **167**, 151 (1947).



Kaiser¹²⁵ converted the fluorescent compound into the presumed monomethyl derivative (**105**). These structures were, however, shown to be incorrect by several different groups of workers (Scheme 2).

Kröhnke¹²⁶ synthesized compound **106** by an unequivocal route starting with a 3,4-disubstituted pyridine and showed that the product was identical with the fluorescent compound described by Huff. Ikekawa¹⁰ converted compound **101** (R=CH₃) into **107** with POCl₃, and then into **102** (R=CH₃), which was shown to be different from 7-methyl-1,6-naphthyridine which he had previously prepared. In the meantime, Birkofer and Kaiser¹²⁷ retracted their earlier structure assignment of material **104** because oxidation of Huff's fluorescent compound with nitric acid gave pyridine-3,4-dicarboxylic acid (**108**).

The treatment of 3-cyano-4-styrylpyridine (**109**) with polyphosphoric acid gave substance **110**. This cyclization represents a rare example of an intramolecular Ritter reaction.¹²⁸ This derivative was converted into compound **111** by the steps outlined. A similar condensation involving the treatment of compound **112** with polyphosphoric acid afforded 1,8-dihydroxy-3,6-diphenyl-2,7-naphthyridine (**113**) in 65% yield.¹²⁹

Cyclization of the condensation product of malononitrile and diethyl adipate derivatives have been used to form the 2,7-naphthyridine ring skeleton (**115**).¹³⁰

¹²⁵ L. Birkofer and C. Kaiser, *Angew. Chem.* **68**, 378 (1956).

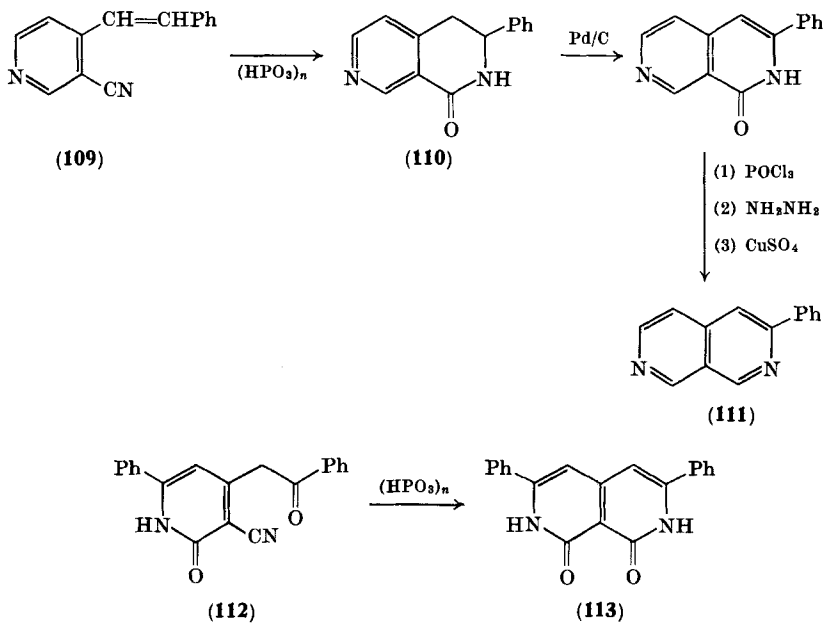
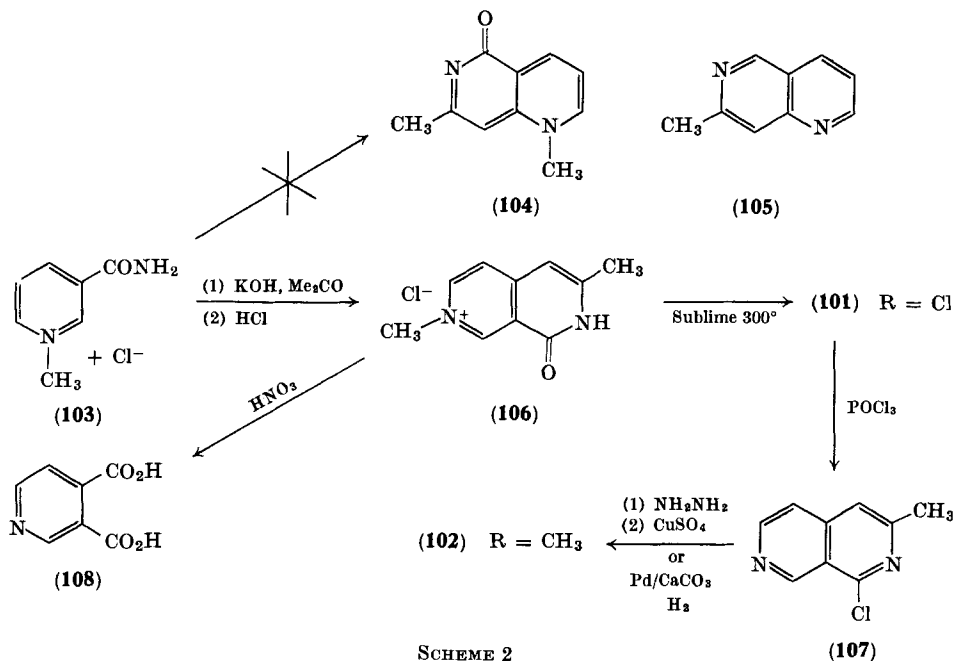
¹²⁶ F. Kröhnke, K. Ellegast, and E. Bertram, *Ann. Chem.* **600**, 198 (1957).

¹²⁷ L. Birkofer and C. Kaiser, *Chem. Ber.* **90**, 2933 (1957).

¹²⁸ J. M. Bobbitt and R. E. Doolittle, *J. Org. Chem.* **29**, 2298 (1964).

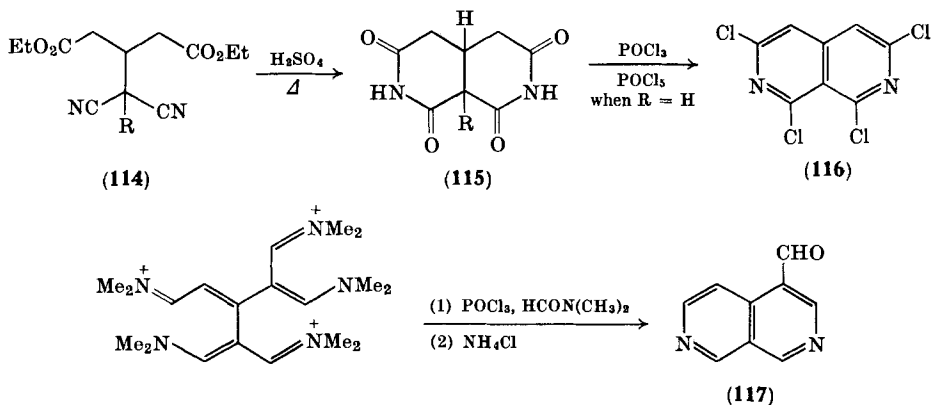
¹²⁹ S. G. Boatman, T. Harris, and C. R. Hauser, *J. Am. Chem. Soc.* **87**, 5198 (1965).

¹³⁰ B. M. Iselin and K. Hoffmann, *J. Am. Chem. Soc.* **76**, 3220 (1954).



Reduction of compound **115** with lithium aluminum hydride afforded the perhydro derivative in good yield. A variety of 1,3,6,8-tetrasubstituted derivatives of 2,7-naphthyridine have been prepared by displacement of the chlorine atoms of compound **116**.¹³¹

The preparation of 2,7-naphthyridine-4-carboxaldehyde (**117**) has been reported by the novel cyclization reaction below.^{132, 133}



IV. General Reactions

A. REDUCTION

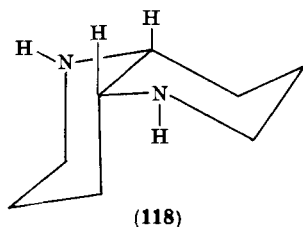
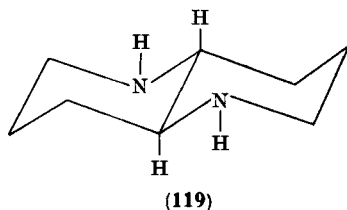
The results of reduction of the naphthyridines are listed in Table X. In the cases of monomethyl and dimethyl derivatives, in general, the nonmethylated pyridine ring is preferentially reduced catalytically to afford the tetrahydro compounds. This phenomenon can be explained by simply suggesting that the methyl groups inhibit the approach of one side of the molecule to the surface of the catalyst. It is interesting to note that when the methyl group is farthest removed from the nitrogen atom (e.g., 4-methyl-1,6-naphthyridine and 4-methyl-1,8-naphthyridine) mixtures of tetrahydro compounds with either one of the rings being reduced are obtained. This suggests that coordination of the molecule with the metal catalysts may take place through the nitrogen atom.

The reduction with sodium and alcohol leads to reduction of both rings, and Armarego⁴⁴ has recently shown that this method affords

¹³¹ B. M. Ferrier and N. Campbell, *J. Chem. Soc.* 3513 (1960).

¹³² Z. Arnold and A. Holly, *Collection Czech. Chem. Commun.* **28**, 2040 (1963).

¹³³ C. Jutz, W. Mueller, and E. Mueller, *Chem. Ber.* **99**, 2479 (1966).

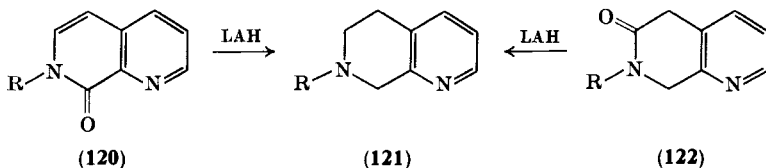
*cis*-Decahydro-1,5-naphthyridine*trans*-Decahydro-1,5-naphthyridine

the *trans* (ring fusion) isomers. The *cis*- and *trans*-decahydro-1,5-naphthyridines (**118** and **119**) have been prepared (see Table X) and their structures have been assigned by comparison of their PMR spectra with those of the *cis*- and the *trans*-decahydroquinolines and decahydroisoquinolines. The structures of *trans*-decahydro-1,6-, *trans*-decahydro-1,7-, and *trans*-decahydro-1,8-naphthyridine were similarly determined.

The dehalogenation of naphthyridines with hydrogen over palladium on calcium carbonate in a weakly basic alcoholic solution gives excellent yields (90–95%) of reduced compounds.^{38, 45, 134, 137, 138} This method for removal of halogens has been extensively used and generally surpasses the classic hydrazine–copper sulfate reduction method.

The use of other metal catalysts in attempted reductions of halonaphthyridines has resulted in reduction of the ring or, at best, in the formation of mixtures.

Lithium aluminum hydride (LAH) has been used¹³⁹ to prepare the tetrahydro-1,7-naphthyridine (**121**) from either compound **120** or **122**.



¹³⁴ K. Miyaki, *J. Pharm. Soc. Japan* **62**, 26 (1942); *Chem. Abstr.* **45**, 627 (1951).

¹³⁵ N. Ikekawa, *Chem. Pharm. Bull. (Tokyo)* **6**, 408 (1958).

¹³⁶ E. Ochiai and K. Miyaki, *Chem. Ber.* **74**, 1115 (1941).

¹³⁷ S. Okuda, *Chem. Pharm. Bull. (Tokyo)* **5**, 460 (1957).

¹³⁸ For other examples, see Weiss and Hauser².

¹³⁹ S. Yoshinobu, *Chem. Pharm. Bull. (Tokyo)* **8**, 427 (1960); *Chem. Abstr.* **55**, 12401 (1961).

TABLE X
REDUCTION OF SOME NAPHTHYRIDINES

Naphthyridine	Method	Product and stereo-chemistry ^a	Yield (%)	Ref.
1,5-Naphthyridines				
Unsubstituted	Na/ethanol	<i>trans</i> -Decahydro	93	44
	H ₂ /PtO ₂ , HOAc or Raney Ni, cyclohexane	1,2,3,4-Tetrahydro	(-)	66
	H ₂ /PtO ₂ , HOAc	<i>trans</i> -Decahydro	12	44
		<i>cis</i> -Decahydro	21	44
	H ₂ /Pd/C, EtOH	1,2,3,4-Tetrahydro	90	44
	H ₂ /PtO ₂ , EtOH	1,2,3,4-Tetrahydro	95	17
2-Methyl	PtO ₂ or Raney Ni	5,6,7,8-Tetrahydro	(-)	66
2-Methyl-5,6,7,8-tetrahydro	Na/amyl alcohol	Decahydro	(-)	66
1,2,3,4-Tetrahydro	Na/amyl alcohol	Hexahydro ^b		66
4-Methyl	H ₂ /PtO ₂ , EtOH	5,6,7,8-Tetrahydro	92	17
2,4-Dimethyl	H ₂ /PtO ₂ or Raney Ni	5,6,7,8-Tetrahydro	(-)	66
2,4-Dimethyl-5,6,7,8-tetrahydro	Na/amyl alcohol	Decahydro	(-)	66
4-Hydroxy	Na/ethanol	<i>trans</i> -Decahydro	35	17
1,6-Naphthyridines				
Unsubstituted	H ₂ /Pd/CaCO ₃	1,2,3,4-Tetrahydro	76	135
	H ₂ /Pd/C, EtOH	1,2,3,4-Tetrahydro	75	44
	H ₂ /PtO ₂ , EtOH	1,2,3,4-Tetrahydro	93	17
	Na/ethanol	<i>trans</i> -Decahydro	65	44

4-Methyl	H ₂ /PtO ₂ , EtOH	1,2,3,4-Tetrahydro	50	17
		5,6,7,8-Tetrahydro	50	17
7-Methyl	H ₂ /Pd/CaCO ₃	1,2,3,4-Tetrahydro	(-)	135
5,7-Dimethyl	H ₂ /Pd/C, MeOH	1,2,3,4-Tetrahydro	76	86
1,7-Naphthyridines				
Unsubstituted	H ₂ /Pd/CaCO ₃	1,2,3,4-Tetrahydro	98	8
		5,6,7,8-Tetrahydro	2	8
	H ₂ /Pd/C, EtOH	1,2,3,4-Tetrahydro	57	44
		5,6,7,8-Tetrahydro	43	44
	Na/ethanol	<i>trans</i> -Decahydro	67	44
1,8-Naphthyridines				
Unsubstituted	Na/ethanol	<i>trans</i> -Decahydro	40	17
1,2,3,4-Tetrahydro	Na/ethanol	<i>trans</i> -Decahydro	50	44
4-Methyl	H ₂ /PtO ₂ , HOAc	5,6,7,8-Tetrahydro	80	134, 136
		1,2,3,4-Tetrahydro	20	134, 136
4-Methyl-5,6,7,8-tetrahydro or -1,2,3,4-tetrahydro	Na/amyl alcohol	Decahydro	(-)	136
2,4-Dimethyl	H ₂ /PtO ₂ , HOAc or Raney Ni, cyclohexane	5,6,7,8-Tetrahydro	98 and 83	136
2,4-Dimethyl-5,6,7,8-tetrahydro	Na/amyl alcohol	Decahydro	(-)	136
2,7-Naphthyridines				
Unsubstituted	H ₂ /Pd/CaCO ₃	1,2,3,4-Tetrahydro	(-)	135
3-Methyl	H ₂ /Pd/CaCO ₃	5,6,7,8-Tetrahydro	88	135
		1,2,3,4-Tetrahydro	12	135

^aYields and stereochemistry are given when reported.

^bPosition of hydrogen atoms not given.

B. SUBSTITUTION REACTIONS

1. *General Considerations*

The naphthyridines, like naphthalene, have ten delocalized π electrons located in five molecular orbitals. Unlike naphthalene, however, but similar to pyridine, each of these orbitals is distorted with an electron drift toward the nitrogen atoms. The positions α and γ to the nitrogen atom have lower π -electron densities than the similar positions in naphthalene, whereas the electron density β to the nitrogen atom, in general, remains about the same as (cf. Section II, B) the equivalent position in naphthalene. Thus, for nucleophilic substitution one would expect the sites α and γ to the nitrogen atoms to be the preferred positions of attack, whereas electrophilic attack should occur at a nitrogen atom, to give a charged species. Although the absolute values of the π -electron densities are certainly different for a charged ion, the relative distribution of electron density at the ring carbon atoms remains almost unchanged in the naphthyridines. Therefore, no matter if electrophilic attack at carbon occurs upon the charged species or the free base, substitution should occur at a position β to a ring nitrogen atom.

The molecular orbital calculations (see Section II, B) are in general agreement with these expectations.

a. *Bromination.* The reaction of 1,5-naphthyridine with bromine in cold chloroform is reported to give a salt which on heating in water affords 1,5-naphthyridin-4-one (**15**) and 1,5-naphthyridine.⁶⁰ The salt is suggested to be the 4-naphthyridylnaphthyridinium bromide hydrobromide.

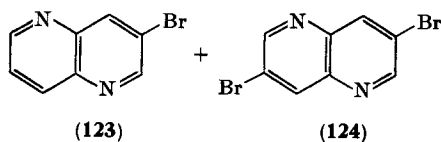
Czuba,^{140, 141} using very severe conditions ($\text{Br}_2\text{-H}_2\text{SO}_4\text{-SO}_3$; 135° , for 45 hours), brominated 1,5-naphthyridine to 3-bromo- (**123**) and 3,7-dibromo-1,5-naphthyridines (**124**), in 10 and 35% yields, respectively.

Recently, Eisch's¹⁴² bromination method ($\text{Br}_2\text{-CCl}_4\text{-pyridine}$) has been applied to all the 1, x -naphthyridines ($x=5, 6, 7, 8$).⁹⁶ 1,5-Naphthyridine afforded 3-bromo- (27%) and 3,7-dibromo-1,5-naphthyridine (10%). The 3-bromo-, 8-bromo-, and 3,8-dibromo-1,6-naphthyridines were obtained from 1,6-naphthyridine.⁹⁶ 1,7-

¹⁴⁰ W. Czuba, *Roczniki Chem.* **37**, 1589 (1963); *Chem. Abstr.* **60**, 8005 (1964).

¹⁴¹ W. Czuba, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **11**, 375 (1963); *Chem. Abstr.* **60**, 2917 (1964).

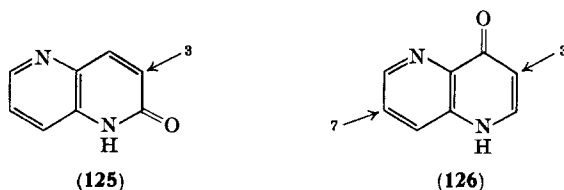
¹⁴² J. J. Eisch, *J. Org. Chem.* **27**, 1318 (1962).



Naphthyridine gave the 5-bromo- and 3,5-dibromo-1,7-naphthyridine. Surprisingly, no 3-bromo-1,7-naphthyridine was detected. Treatment of 1,8-naphthyridine under the same conditions gave by far the lowest yield of bromo products, the 3-bromo- (5%) and the 3,6-dibromo-1,8-naphthyridine (0.5%). The low yield is, perhaps, attributable to the strong complexing properties of 1,8-naphthyridine (see Section IV, C).

The bromination and bromodehydroxylation of hydroxynaphthyridines under a variety of conditions have been reported.

Treatment of 1,5-naphthyridin-2-one (**125**) with bromine and water gave the 3-bromo product. Similarly, the 1,5-naphthyridin-4-one (**126**) afforded the 3-bromo compound under the same conditions.⁶⁴ The 4-oxo compound (**126**) when reacted with phosphorus pentabromide afforded 3,4,8-tribromo-1,5-naphthyridine. The reaction of compound **126** with phosphorus oxybromide gave the expected 4-bromo compound.



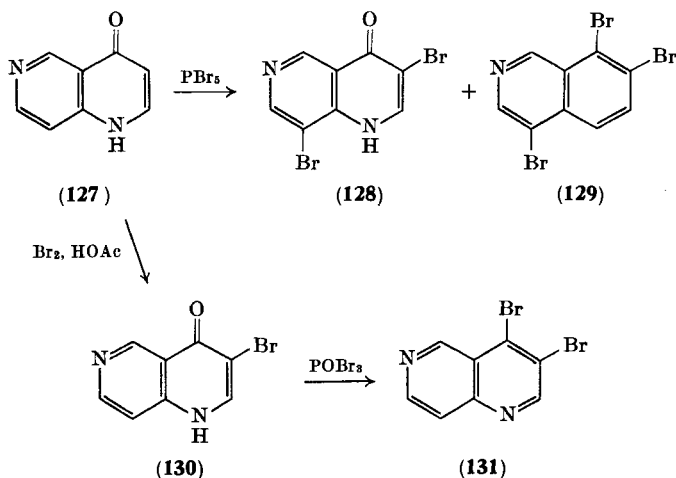
Two products (**128** and **129**) were obtained when 1,6-naphthyridin-4-one (**127**) reacted with phosphorus pentabromide.¹⁴³ It is presumed that **128** is the precursor of **129**. The 4-bromo derivative was obtained when compound **127** was treated with phosphorus oxybromide. The 3-bromo-1,6-naphthyridin-4-one (**130**) was prepared in good yield from compound **127**, and on reaction with phosphorus oxybromide the 3,4-dibromo-1,6-naphthyridine (**131**) could be obtained. The reaction of 1,7-naphthyridin-8-one with phosphorus oxybromide is unique,¹⁴⁴ since it appears to be the only example in this series, in which further bromination occurs with this reagent, affording 8-monobromo and 3,8-dibromo-1,7-naphthyridine.

¹⁴³ W. W. Paudler and T. J. Kress, *J. Heterocyclic Chem.* **2**, 292 (1965).

¹⁴⁴ W. W. Paudler and T. J. Kress, unpublished results (1968).

b. *Nitration*. The nitration of 1,5-naphthyridine using a range of concentrated and fuming acids was unsuccessfully attempted by Hart.⁶⁰ Hydorn¹⁴⁵ failed to nitrate both the mono- and the di-*N*-oxides of 1,5-naphthyridine.

The treatment of 4-methyl-1,8-naphthyridine-2,7-dione with fuming nitric and sulfuric acids is reported to give a mononitro derivative of uncertain structure.¹⁴⁶



The nitration of 1,5-naphthyridin-2- and -4-one gave, in both cases, the 3-nitro derivative.⁶⁴ The 2-oxo-3-nitro- and the 5-oxo-8-nitro-1,6-naphthyridines were obtained by Albert and Armarego⁵⁸ from the corresponding parent oxo compounds under nitrating conditions.

2. Nucleophilic Substitution

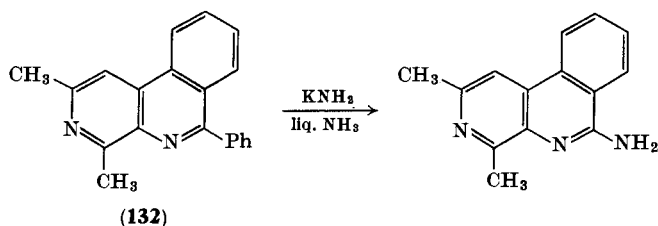
a. *Amination*. The amination of 1,5-naphthyridine with sodium amide has been described by Hart⁶⁰ and was shown to give the 2-amino derivative. Later workers,⁹⁶ however, were unable to repeat this amination under the specified conditions, but employed a different procedure which was successfully used to aminate all the 1,*x*-naphthyridines ($x=5,6,7,8$). Thus, the amination of 1,5-naphthyridine with potassium amide in liquid ammonia at room temperature in a

¹⁴⁵ A. Hydorn, Ph.D. Thesis, University of Michigan, Ann Arbor, Michigan (1960).

¹⁴⁶ A. Mangini, *Boll. Sci. Fac. Chim. Ind. Bologna Suppl.*, 165 (1940); *Chem. Abstr.* 36, 5476 (1942).

sealed tube gave a 33% yield of 2-amino-1,5-naphthyridine. Similarly, the 1,6- and the 1,8-naphthyridine gave the 2-amino compound (45 and 30%), while the 1,7-naphthyridine afforded the 8-amino derivative (56%).

An interesting amination, apparently involving displacement of a phenyl group in the benzo[c]1,7-naphthyridine (132)¹⁴⁷ has been reported.



b. *Displacement of Halogens in Naphthyridines.* The number of reactions involving displacement of a halogen atom of a substituted naphthyridine are legion and only those in which a systematic investigation has been made will be discussed in this section.¹⁴⁸

It has been demonstrated that the 2-chlorine atom in 2,4-dichloro-1,5-naphthyridine can be preferentially displaced by water, ammonia, and hydrazine. With phenol, aniline, and benzylamine, both chlorine atoms are replaced. The selective reactivity of the 2-chlorine atom is in agreement with approximate quantum mechanical calculations.²⁵

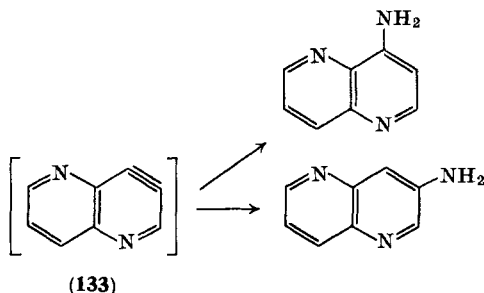
The reaction of the tribromo-1,6-naphthyridine (129) with sodium methoxide causes selective replacement of the 4-bromine atom.³⁹ This result is, of course, expected.

Czuba⁶⁷ prepared 2-, 3-, and 4-bromo-1,5-naphthyridine and treated them with potassium amide in liquid ammonia. The results of this study were explained by the intermediacy of 1,5-naphthyridyne-3,4 (133)¹⁴⁹ in the reaction of the 3- and 4-bromo derivatives. A competing addition-elimination mechanism was also suggested since the ratios of the amino products from the 3- and 4-bromo compounds were not the same.¹⁴⁷

¹⁴⁷ S. S. Berg and V. Petrow, *J. Chem. Soc.* 3713 (1952).

¹⁴⁸ Nucleophilic substitutions in naphthyridines are dealt with by R. G. Shepherd and J. L. Fedrick, *Advan. Heterocyclic Chem.* **4**, 377-382 (1965).

¹⁴⁹ The 1,5-naphthyridynes have been considered in detail by H. J. den Hertog and H. C. van der Plas, *Advan. Heterocyclic Chem.* **4**, 139 (1965).

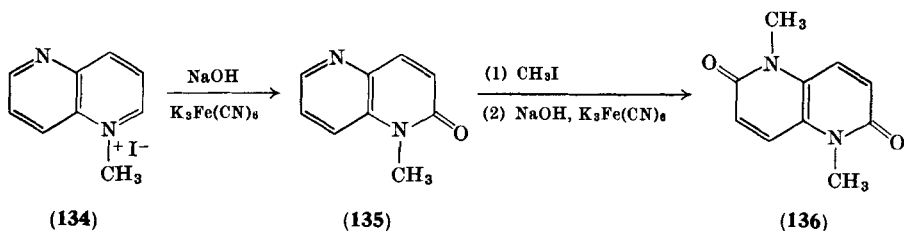


C. REACTIONS ON NITROGEN

1. Formation and Reactions of Quaternary Salts

As previously mentioned, the quaternization of the naphthyridines has been considered by Duffin,³ and the reader should refer to this work for additional references.

The reaction of 1,5-naphthyridine with methyl iodide gave, as expected, the monomethiodide (134). Oxidation of the salt, under basic conditions, with potassium ferricyanide, afforded the *N*-methyl naphthyridinone (135).¹⁶ Repetition of this sequence yielded,

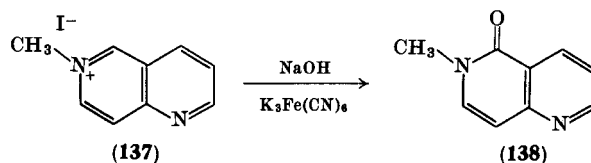


ultimately, compound 136.¹⁶ The methiodide salt of 2-methyl-6-chloro-1,5-naphthyridine has been prepared and the 1-methyl structure was assigned by Duffin.³

A diquaternary salt of 1,5-naphthyridine was prepared by refluxing the parent compound in dimethyl sulfate.¹⁵⁰

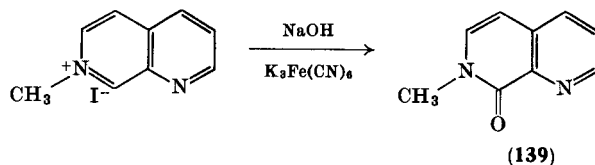
Quaternization of 1,6-naphthyridine with methyl iodide takes place at the 6-nitrogen atom.⁵⁶ The position of methylation was proven by the structure determination of the alkaline oxidation product (138) obtained from the salt (137).

¹⁵⁰ L. A. Summers and J. E. Dickeson, *Chem. Commun.* 1183 (1967).

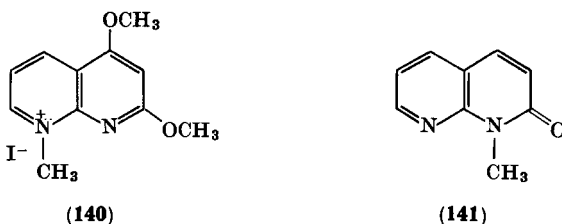


1,6-Naphthyridin-8-one was suggested to be methylated at the 6-nitrogen atom since the salt is still able to form a nickel complex.⁵⁴ This suggestion has been confirmed by Sigel and Kaden¹⁵¹ by the similarity of a series of stability constants for structurally related complexes.

The structure of the basic oxidation product of the monomethiodide salt of 1,7-naphthyridine has been shown by PMR spectroscopy to be 7-methyl-8-oxo-7,8-dihydro-1,7-naphthyridine (**139**).⁵⁶ Thus, methylation of this ring system takes place at N-7.



Methylation of 2,4-dimethoxy-1,8-naphthyridine was shown to take place at N-8 [to give (**140**)], by potassium ferricyanide oxidation to the appropriate *N*-methyl naphthyridinone.¹⁵² Similarly, treatment of the monomethiodide of 1,8-naphthyridine gave the expected naphthyridin-2-one (**141**).⁵⁶



2. Formation and Reactions of *N*-Oxides

The chemistry of the mono- and of the di-*N*-oxides of the naphthyridines has been the subject of only minor consideration and

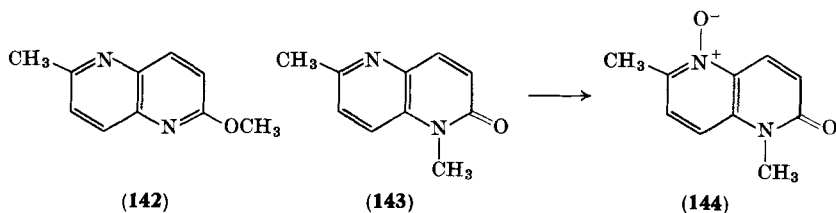
¹⁵¹ H. Sigel and T. Kaden, *Helv. Chim. Acta* **49**, 1617 (1966).

¹⁵² G. Koller and E. Kandler, *Monatsh. Chem.* **58**, 213 (1931).

remains relatively unknown. Both the mono- and the di-*N*-oxides of 1,5-naphthyridine have been prepared by direct oxidation (peracetic acid or hydrogen peroxide-acetic acid mixtures) of the parent substance.⁶⁰

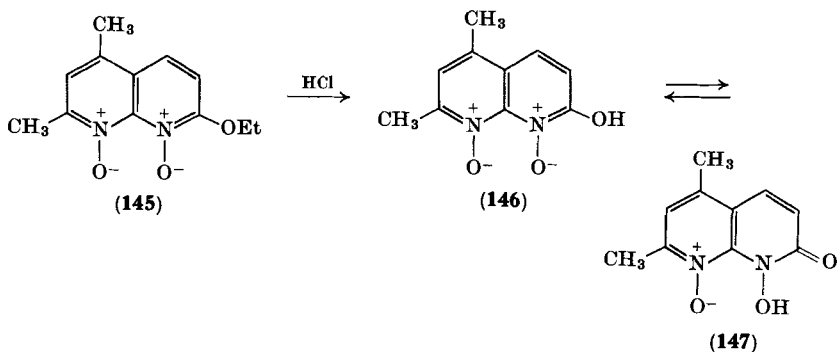
Similar to the reaction of the *N*-oxides of pyridine and quinoline, 1,5-naphthyridine 1-oxide undergoes the Meisenheimer reaction to afford roughly equal amounts of 2-chloro- and 4-chloro-1,5-naphthyridine.¹⁵³ Only the 2,6-dichloro-1,5-naphthyridine was isolated from the same reaction with the di-*N*-oxide.⁶⁰ Certainly, a more detailed investigation of this reaction is warranted in view of the results from the mono-*N*-oxide.

The reaction of **142** with hydrogen peroxide and acetic acid afforded a mono-*N*-oxide. However, the position of the *N*-oxide function was not established.⁷⁰ The 1,6-dimethyl-2-naphthyridinone (**143**) on similar treatment gave the 5-oxide (**144**).⁷⁰



For the preparation of 1,6-naphthyridine *N*-oxide by the cyclization of pyridine *N*-oxides, see Section III, B.

A substituted 7-oxide (**54**) (see Section III, C) of 1,7-naphthyridine has been prepared by the condensation and cyclization of 3-amino-pyridine with EMME.



¹⁵³ E. V. Brown and A. C. Plaszc, *J. Org. Chem.* **32**, 241 (1967).

The 1,8-naphthyridine di-*N*-oxide (**145**), was prepared by oxidation of the corresponding base.¹⁵⁴ Hydrolysis of **145** gave the 2-hydroxy derivative (**146**) in equilibrium with the cyclic hydroxamic acid (**147**).¹⁵⁵

3. Coordination Compounds

Metal complexes, analogous to 8-hydroxyquinoline,^{54, 151} of 4-hydroxy-1,5-naphthyridine,⁵⁴ 8-hydroxy-1,6-naphthyridine,^{54, 151} and 8-hydroxy-1,7-naphthyridine⁵⁴ with Cu(II), Ni(II), Fe(II), and Fe(III) have been prepared. The hydroxynaphthyridines chelate less readily than 8-hydroxyquinoline since they are weaker bases.¹⁵¹

Unsubstituted 1,5-naphthyridine has been shown to form complexes of the type ML_2 , where M is Cu(II), Co(II), Ni(II), and L is 1,5-naphthyridine.¹⁵⁶ Coordination compounds of this type involving Cd(II), Pd(II), Ba(II), and Zn(II) could not be prepared with 1,5-naphthyridine.

Metal carbonyl complexes of the type $M(CO)_4L$, where M = Cr, Mo, or W and L is the bidentate 2,7-dimethyl-1,8-naphthyridine, have recently been prepared by Hendricker and Reed.¹⁵⁷

D. PHOTOCHEMISTRY

3-Amino-1,6-naphthyridin-4-one (**148**), upon irradiation with UV light in the presence of sodium nitrite loses nitrogen to afford the 3-carboxy-5-azaindole (**149**).^{85, 158} This reaction has also been carried out on the corresponding derivatives of 1,7-naphthyridine^{158, 159} and 7-carboxy-1,8-naphthyridine⁸⁵ to give the expected 1,6- and 1,7-azaindoles.

¹⁵⁴ M. Colonna and A. Risaliti, *Boll. Sci. Fac. Chim. Ind. Bologna* **9**, 82 (1951); *Chem. Abstr.* **46**, 7102 (1952).

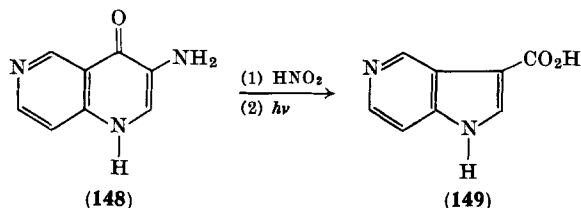
¹⁵⁵ M. Colonna and C. Runti, *Gazz. Chim. Ital.* **82**, 513 (1952); *Chem. Abstr.* **48**, 680 (1954).

¹⁵⁶ T. D. Eck, E. L. Wehry, and D. M. Hercules, *J. Inorg. Nucl. Chem.* **28**, 2439 (1966).

¹⁵⁷ D. G. Hendricker and T. E. Reed, 1st Central Reg. Meeting Am. Chem. Soc. Akron, Ohio (1968).

¹⁵⁸ T. Alder and A. Albert, *J. Chem. Soc.* p. 1794 (1960).

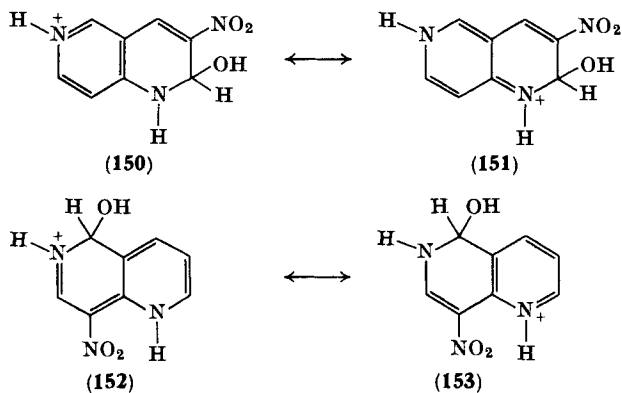
¹⁵⁹ O. Süs and K. Möller, *Ann. Chem.* **599**, 233 (1956).



E. COVALENT HYDRATION

Covalent hydration in the naphthyridines has been considered in comprehensive reviews.^{160, 161} Although no evidence could be obtained for covalent hydration in the neutral species or cations of 1,5-, 1,6-, 1,7-, and 1,8-naphthyridine, the 3-nitro- and 8-nitro-1,6-naphthyridine cations readily undergo hydration. 3-Nitro-1,5-naphthyridine, on the other hand, is not hydrated.

The added electron deficiency at positions 2 and 5 in the nitro-1,6-naphthyridines together with the resonance stabilization of the hydrated cations ($150 \leftrightarrow 151$; $152 \leftrightarrow 153$) is thus required for covalent hydration. The 3-nitro-1,5-naphthyridine satisfies the first requirement, but not the latter, and indeed is not hydrated.⁵⁸



V. Uses

Since the discovery, in 1962, by Leshner and co-workers¹⁶² that 1-ethyl-3-carboxy-7-methyl-1,8-naphthyridin-4-one (nalidixic acid, **154**) is a powerful antibacterial agent, numerous publications have

¹⁶⁰ A. Albert and W. L. F. Armarego, *Advan. Heterocyclic Chem.* **4**, 18 (1965).

¹⁶¹ A. Albert, *Angew. Chem.* **79**, 913 (1967).

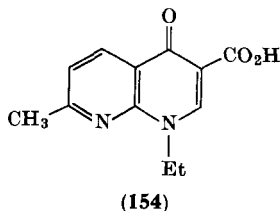
¹⁶² G. Y. Leshner, E. J. Froelich, M. D. Gruett, J. H. Bailey, and R. P. Brundage, *J. Med. Pharm. Chem.* **5**, 1063 (1962).

appeared describing its derivatives,¹⁶³⁻¹⁶⁸ detection,¹⁶⁹⁻¹⁷³ and physiological and chemical properties.¹⁷⁴⁻¹⁸⁹ The new drug has been shown to be particularly effective against gram-negative bacteria¹⁹⁰⁻²²⁰ found in chronic urinary tract infections.

- ¹⁶³ Z. Meszaros, G. Kovacs, P. Szentmiklosi, and I. Czibula, Hungarian Patent 153,292 (1966); *Chem. Abstr.* **67**, 64379 (1967).
- ¹⁶⁴ R. Aries, French Patent 1,439,581 (1965); *Chem. Abstr.* **65**, 18591 (1966).
- ¹⁶⁵ G. Y. Leshner and M. D. Gruett, Belgian Patent 612,258 (1962); *Chem. Abstr.* **58**, 7953 (1963).
- ¹⁶⁶ Bonaplata Laboratories, Spanish Patent 316,061 (1965); *Chem. Abstr.* **64**, 12679 (1966).
- ¹⁶⁷ E. D. Nielson, P. B. Hamilton, D. Rosi, and G. P. Peruzzoth, French Patent 1,450,424 (1966); *Chem. Abstr.* **66**, 54279 (1967).
- ¹⁶⁸ M. Aceto, L. Harris, G. Y. Leshner, J. Pearl, and T. Brown, *J. Pharmacol. Exptl. Therap.* **158**, 286 (1967); *Chem. Abstr.* **67**, 115640 (1967).
- ¹⁶⁹ I. Dick and N. Murgu, *Rev. Chim. (Bucharest)* **15**, 757 (1964); *Chem. Abstr.* **62**, 15600 (1965).
- ¹⁷⁰ V. Ignat and H. Beral, *Rev. Chim. (Bucharest)* **17**, 50 (1966); *Chem. Abstr.* **64**, 17360 (1966).
- ¹⁷¹ M. J. J. Vieira da Silva and M. T. C. Nogueira, *Rev. Port. Farm.* **15**, 290 (1965); *Chem. Abstr.* **64**, 9513 (1966).
- ¹⁷² N. Murgu, *Pharmazie* **19**, 724 (1964); *Chem. Abstr.* **62**, 7591 (1965).
- ¹⁷³ G. Dondi and M. DiMarco, *Boll. Chim. Farm.* **105**, 491 (1966); *Chem. Abstr.* **65**, 20112 (1966).
- ¹⁷⁴ G. Y. Leshner, *Intern. 3rd Congr. Chemotherapy, Proc., Stuttgart*, 1963 Vol. 2, 1367. Thieme, Stuttgart, 1964; *Chem. Abstr.* **65**, 15925 (1966).
- ¹⁷⁵ H. Seneca, *J. Am. Geriatr. Soc.* **12**, 1100 (1964); *Chem. Abstr.* **62**, 8257 (1965).
- ¹⁷⁶ W. A. Goss, W. H. Deitz, and T. M. Cook, *J. Bacteriol.* **89**, 1068 (1965).
- ¹⁷⁷ H. S. Roseneranz and C. Lambek, *Proc. Soc. Exptl. Biol. Med.* **120**, 549 (1965); *Chem. Abstr.* **64**, 4115 (1966).
- ¹⁷⁸ W. H. Deitz, T. M. Cook, and W. A. Goss, *J. Bacteriol.* **91**, 768 (1966).
- ¹⁷⁹ A. Bauernfeind and G. Gruemmer, *Chemotherapia* **10**, 95 (1965); *Chem. Abstr.* **64**, 10114 (1966).
- ¹⁸⁰ A. Taketo and H. Watanabe, *J. Biochem. (Tokyo)* **61**, 520 (1967); *Chem. Abstr.* **67**, 8828 (1967).
- ¹⁸¹ J. V. Boyle, W. A. Goss, and T. M. Cook, *J. Bacteriol.* **94**, 1664 (1967).
- ¹⁸² H. Lyman, *J. Cell Biol.* **35**, 726 (1967).
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- ¹⁸⁶ H. Friesewinkel, R. Reimann-Hunziker, and G. J. Reimann-Hunziker, *Intern. 3rd Congr. Chemotherapy, Proc., Stuttgart*, 1963 Vol. 2, p. 1385. Thieme, Stuttgart, 1964; *Chem. Abstr.* **65**, 14140 (1966).

- 187 I. V. Lishman, *Intern. 3rd Congr. Chemotherapy, Proc., Stuttgart*, 1963 Vol. 2, p. 1379. Thieme, Stuttgart, 1964; *Chem. Abstr.* **65**, 6156 (1966).
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- 202 T. M. Cook, K. G. Brown, J. V. Boyle, and W. A. Goss, *J. Bacteriol.* **92**, 1510 (1966).
- 203 S. Nakazawa, K. Nakamura, Y. Niwa, and M. Yoko, *Nippon Kagaku Ryohogakukai Zasshi* **13**, 139 (1965); *Chem. Abstr.* **64**, 18060 (1966).
- 204 Y. Kanazawa and T. Kuramata, *J. Antibiotics (Tokyo)* **B19**, 31 (1966); *Chem. Abstr.* **65**, 10996 (1966).
- 205 W. Stille and K. H. Ostner, *Klin. Wochschr.* **44**, 155 (1966).
- 206 A. M. Barlow, *Intern. 3rd Congr. Chemotherapy, Proc., Stuttgart*, 1963 Vol. 2, p. 1374. Thieme, Stuttgart, 1964; *Chem. Abstr.* **65**, 11214 (1966).
- 207 E. N. Padeiskaya and G. N. Pershin, *Antibiotiki* **11**, 141 (1966); *Chem. Abstr.* **65**, 2852 (1966).
- 208 J. E. Martin, Jr., J. D. Thayer, S. B. Samuels, and J. B. Lucas, *Antimicrobial Agents Chemotherapy* p. 366 (1965).
- 209 C. VanMarwyck and B. Warnecke, *Arzneimittel-Forsch.* **16**, 494 (1966); *Chem. Abstr.* **65**, 2668 (1966).
- 210 H. Warenbourg and G. Stalnikiewicz, *Lille Med.* **11**, 1201 (1966); *Chem. Abstr.* **66**, 84549 (1967).
- 211 H. Aratani, A. Nakagawa, T. Hiromi, T. Hashimoto, and S. Nakamura, *Nippon Kagaku Ryohogakukai Zasshi* **14**, 347 (1966); *Chem. Abstr.* **66**, 9711 (1967).

Several 1,5-,⁷² 1,6-,²²¹ 1,7-,²²² and 1,8-naphthyridines²²³ have been screened for antimalarial activity, with some activity reported in the 1,7-naphthyridine series.

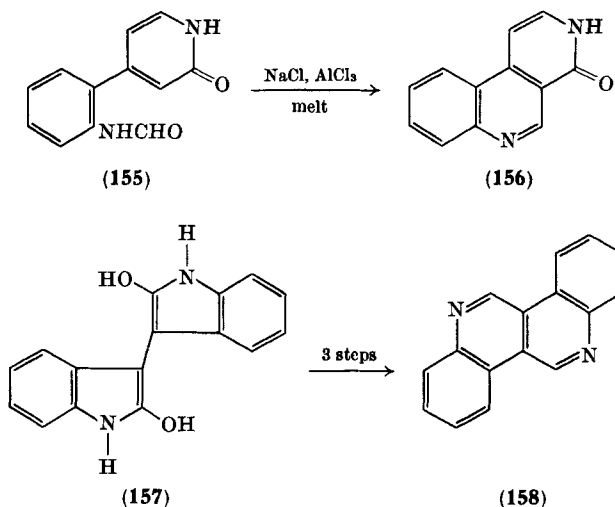


The naphthyridines have also been described as useful in the analytical determination of iron(III)²²⁴ and as bacteriocides,^{54, 57, 225-232} antioxidants,²³³ hypotensive agents,²³⁴ dyes,^{235, 236} and antituberculars.²³⁷ The presence of some naphthyridines in polymers made from acrylonitrile was reported.²³⁸

- ²¹² O. Kitamoto, K. Fukaya, and T. Wajima, *Nippon Kagaku Ryohogakukai Zasshi* **14**, 337 (1966); *Chem. Abstr.* **66**, 9663 (1967).
²¹³ H. Beerhens and M. M. Tahon-Castel, *Ann. Inst. Pasteur* **111**, 90 (1966); *Chem. Abstr.* **66**, 646 (1967).
²¹⁴ S. Goto, *et al.*, *Nippon Kagaku Ryohogakukai Zasshi* **14**, 377 (1966); *Chem. Abstr.* **66**, 93925 (1967).
²¹⁵ A. R. Ronald, M. Jurck, and R. G. Petersdorf, *New Engl. J. Med.* **275**, 1801 (1966); *Chem. Abstr.* **66**, 9903 (1967).
²¹⁶ S. C. Arya, *Indian J. Med. Res.* **55**, 224 (1967); *Chem. Abstr.* **66**, 113250 (1967).
²¹⁷ K. D. Demidova, V. V. Kazakova, T. I. Kudryashova, M. B. Lis, B. A. Morozov, A. G. Pechenkin, O. E. Pylaeva, E. A. Rudgit, G. Kh. Khismutdinov, and K. E. Chistyakov, *Med. Prom. SSSR* **20**, 18 (1966); *Chem. Abstr.* **66**, 2494 (1967).
²¹⁸ H. W. Smith, *Vet. Record* **80**, 464 (1967); *Chem. Abstr.* **67**, 988 (1967).
²¹⁹ Y. Yokoto, K. Ishida, H. Ishida, K. Tani, and N. Yoshida, *Nippon Kagaku Ryohogakukai Zasshi* **15**, 160 (1967); *Chem. Abstr.* **67**, 8930 (1967).
²²⁰ J. Nezval and K. Halačka, *Experientia* **23**, 1043 (1967).
²²¹ W. W. Paudler and T. J. Kress, unpublished results (1968).
²²² P. Chien and C. C. Cheng, *J. Med. Chem.* **11**, 164 (1968).
²²³ R. Ito, Y. Hashimoto, M. Iida, and M. Hamana, *Symp. Enzyme Chem. (Tokyo)* **4**, 32 (1950); *Chem. Abstr.* **45**, 7166 (1951).
²²⁴ N. Murgu, *Bull. Stiint. Tech. Inst. Politeh. Timișoara* **11**, 493 (1966); *Chem. Abstr.* **68**, 20889 (1968).
²²⁵ W. R. Scholler and O. Schiekh, U.S. Patent 2,002,280 (1935); *Chem. Abstr.* **29**, 4598 (1935).
²²⁶ V. Petrow, British Patent 583,109 (1946); *Chem. Abstr.* **42**, 2403 (1948).

VI. Naturally Occurring Naphthyridines

Perlolidine, a minor alkaloid of rye grass, has been shown to be the benzonaphthyridine derivative (**156**) by its synthesis from the substituted 4-phenylpyridine (**155**).²³⁹



²²⁷ Cilag Ltd., Swiss Patent 263,148 (1949); *Chem. Abstr.* **44**, 6099 (1950).

²²⁸ C. Richter, U.S. Patent 2,517,929 (1950); *Chem. Abstr.* **45**, 672 (1951).

²²⁹ R. Passerini, *Boll. Sci. Fac. Chim. Ind. Bologna* **8**, 138 (1950); *Chem. Abstr.* **45**, 7974 (1951).

²³⁰ R. Passerini, *Rend. Ist. Super. Sanita* **15**, 64 (1952); *Chem. Abstr.* **47**, 6948 (1953).

²³¹ A. A. Goldberg and R. S. Theobald, British Patent 754,348 (1956); *Chem. Abstr.* **50**, 16876 (1956).

²³² G. Y. Leshner and M. D. Gruett, Belgian Patent 612,258 (1962); *Chem. Abstr.* **58**, 7953 (1963).

²³³ N. R. Easton and G. F. Hennion, U.S. Patent 3,331,846 (1967); *Chem. Abstr.* **67**, 99627 (1967).

²³⁴ H. Takagi, K. Kitamura, S. Kobayashi, S. Inada, and T. Katayama, *Takamine Kenkyusho Nempo* **13**, 122 (1961); *Chem. Abstr.* **56**, 10870 (1962).

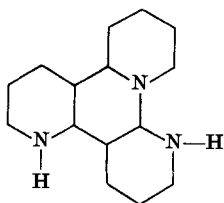
²³⁵ M. Pailer and E. Kuhn, *Monatsh. Chem.* **84**, 85 (1953); *Chem. Abstr.* **47**, 6285 (1953).

²³⁶ P. Dimroth, 100 Jahre BASF aus Forsch. 131 (1965); *Chem. Abstr.* **65**, 2377 (1966).

²³⁷ J. Cymerman-Craig, S. D. Rublo, and B. J. Pierson, *Brit. J. Pathol.* **36**, 254 (1955).

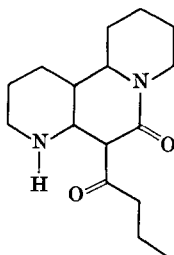
²³⁸ E. A. Aripov, *Uzbeksk. Khim. Zh.* **9**, 52 (1965); *Chem. Abstr.* **66**, 3067 (1967).

²³⁹ R. N. Seelye and D. W. Stanton, *Tetrahedron Letters*, 2633 (1966).

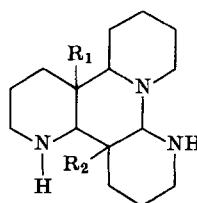
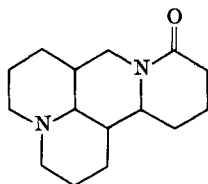


(159)

Alkaloid 1



Alkaloid 2

Alkaloid 3 and 5,
tentatively R₁ or R₂ = OH

(160)

Degradation of the alkaloid calycanthine affords calycanine (**158**) (dibenzo[*c,f*][2,6-]naphthyridine).²⁴⁰ Woodward and co-workers proved the structure of this derivative by an unequivocal synthesis from leucoisindigo (**157**).²⁴⁰

Seven alkaloids have been isolated from *Haloxylon salicornicum* (named 1-7) and four of them have been shown to have a naphthyridine skeleton. Alkaloid 1 (**159**) can be considered as a derivative of either 1,8- or 1,6-naphthyridine, whereas alkaloids 2, 3, and 5, which structurally resemble **159**, are possibly biogenetically related.²⁴¹

Okuda has suggested that some degradation products of matrine (gross structure **160**) are derivatives of 1,2,3,4-tetrahydro-5-methyl-8-propyl-1,6-naphthyridine.²⁴²

²⁴⁰ R. B. Woodward, N. C. Yang, T. J. Katz, V. M. Clark, J. Harley-Mason, R. F. J. Ingleby, and N. Sheppard, *Proc. Chem. Soc.* **76** (1960).

²⁴¹ K. H. Michel, F. Sandberg, F., Haglid, and T. Norin, *Acta Pharm. Suecica* **4**, 97 (1967).

²⁴² S. Okuda, *Chem. Pharm. Bull. (Tokyo)* **4**, 257 (1956); *Chem. Abstr.* **51**, 8087 (1957).

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Recent Advances in the Chemistry of Benzo[*b*]thiophenes

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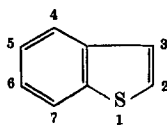
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I. Introduction

The present review deals with the chemistry of benzo[*b*]thiophene (1) from the beginning of 1952 to June 30, 1968.¹ The chemistry of benzo[*b*]thiophene prior to May 1952 has been covered previously in



(1)

the well-known monograph by Hartough and Meisel.² As far as possible we have divided this chapter in such a way that it can be used in conjunction with the previous review to give the reader a complete coverage of the chemistry of benzo[*b*]thiophene to date. Reference to thioindigo chemistry and to work concerned solely with the biological properties of benzo[*b*]thiophene and its derivatives has been omitted. With the exception of a few miscellaneous patents and reactions, our review is comprehensive; we apologize for work overlooked. Lack of space has not allowed us to discuss many important aspects fully.

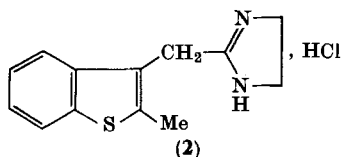
The currently accepted name for **1** in *Chemical Abstracts* is benzo[*b*]thiophene. Thionaphthene (or thianaphthene), 1-thiaindene (particularly in Russian literature) and, less commonly, benzothiofuran

¹ All readily accessible literature has been covered, including all references pertaining to the subject which had appeared up to, and including, Vol. **68** of *Chemical Abstracts* (June 30, 1968).

² H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 17. Wiley (Interscience), New York, 1954.

are also currently used. Octahydrobenzo[b]thiophene and 2,3-dihydrobenzo[b]thiophene are usually referred to as 1-thiahydrindane and 1-thiaindane, respectively. However, we prefer to use the former, systematic, nomenclature. Other points concerning nomenclature are raised at the appropriate place.

Benzo[b]thiophene is available in semicommercial quantities. At times it is difficult to purchase, but it can be readily synthesized from thiophenol (see Section IV). Since 1952, there appears to have been a declining interest in thioindigo dyestuffs. We are not aware of any other major commercial uses of benzo[b]thiophenes, although recently the Mobil Oil Corporation has become interested in 4-benzo[b]thienyl *N*-methylcarbamate (trade name Mobam) and related compounds as pesticides. The commercial interest in benzo[b]thiophene and its derivatives is reflected in the large number of patents that have been published. As with thiophene,^{3,4} many workers have attempted to synthesize compounds with useful biological activity.⁵ At least one drug [Benazoline hydrochloride (2), a nasal decongestant] containing the benzo[b]thiophene nucleus is available commercially,⁶ and several have undergone clinical trial since 1952.



The use of modern physical methods (NMR, UV, and IR spectroscopy, mass spectrometry, and gas-liquid (GLC) and thin-layer (TLC) chromatography) is becoming increasingly noticeable. By 1952² few systematic studies of the preparation of derivatives of benzo[b]thiophene had been undertaken, no attempt had been made to alkylate benzo[b]thiophene by means of the Friedel-Crafts reaction, and Friedel-Crafts acylation had been little studied. Halogenation of benzo[b]thiophene had only been superficially investigated and

³ S. Gronowitz, *Advan. Heterocyclic Chem.* **1**, 1 (1963).

⁴ M. Martin-Smith and S. T. Reid, *J. Med. Pharm. Chem.* **1**, 507 (1959).

⁵ E. Campaigne, T. R. Bosin, and E. S. Neiss, *Advan. Drug Res.* (1969) (in press); a review entitled "Biologically Active Benzo[b]thiophene Derivatives."

⁶ *Drug Trade News* p. 37 (Feb. 12, 1968).

orientation studies in benzo[*b*]thiophene chemistry had been ignored generally. Consequently, some doubtful chemistry had been published. A large number of benzo[*b*]thiophenes are now available by a variety of synthetic routes (see Section IV), but research along the other lines mentioned above has been fairly disappointing; much confusion still exists.

II. Occurrence of Benzo[*b*]thiophenes

A. IN CRUDE PETROLEUM OIL

Benzo[*b*]thiophene and its alkyl derivatives are found in shale oils⁷ and various crude petroleum oils⁸⁻²³; reduced benzo[*b*]thiophenes

- ⁷ H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 19. Wiley (Interscience), New York, 1954.
- ⁸ H. E. Lumpkin and B. H. Johnson, *Anal. Chem.* **26**, 1719 (1954).
- ⁹ S. H. Hastings, B. H. Johnson, and H. E. Lumpkin, *Anal. Chem.* **28**, 1243 (1956).
- ¹⁰ F. P. Richter, A. L. Williams, and S. L. Meisel, *J. Am. Chem. Soc.* **78**, 2166 (1956).
- ¹¹ B. B. Krol, Z. I. Rozanova, and A. A. Rozhdestvenskaya, *Khim. i Tekhnol. Topliv i Masel* **8**, 26 (1963); *Chem. Abstr.* **59**, 361 (1963).
- ¹² B. B. Krol and Z. I. Rozanova, *Khim. Seraorgan. Soedin., Soderzhashch. v Neft. i Nefteprod., Akad. Nauk SSSR, Bashkirsk. Filial* **6**, 42 (1964); *Chem. Abstr.* **61**, 10516 (1964).
- ¹³ Ya B. Chertkov, V. G. Spirkin, and V. N. Demishev, *Neftekhimiya* **6**, 309 (1966); *Chem. Abstr.* **65**, 3636 (1966).
- ¹⁴ H. J. Coleman, C. J. Thompson, R. L. Hopkins, N. G. Foster, M. L. Whisman, and D. M. Richardson, *J. Chem. Eng. Data* **6**, 464 (1961).
- ¹⁵ E. Kado and K. Kado, *Yukagaku* **6**, 273 (1957); *Chem. Abstr.* **55**, 4937 (1961).
- ¹⁶ J. W. Davis, D. E. Hirsch, N. G. Foster, and F. C. Schwartz, *U.S., Bur. Mines, Rept. Invest.* **6298** (1963); *Chem. Abstr.* **59**, 15087 (1963).
- ¹⁷ I. W. Kinney, J. R. Smith, and J. S. Ball, *Anal. Chem.* **24**, 1749 (1952).
- ¹⁸ O. Eisen, E. Arumeel, J. Eisen, H. Raude, I. Poder, O. Kirret, L. Lahe, and P. M. Vaenikver, *Eesti NSV Teaduste Akad. Toimetised, Füüsik.-Mat. ja Tehnikateaduste Seer.* **13**, 135 (1964); *Chem. Abstr.* **62**, 2644 (1965).
- ¹⁹ R. L. Martin and J. A. Grant, *Anal. Chem.* **37**, 644 (1965); *Am. Chem. Soc., Div. Petrol. Chem., Preprints* **10**, C-5 and C-17 (1965).
- ²⁰ A. A. Rozhdestvenskaya, A. G. Siryuk, B. B. Krol, and K. I. Zimina, *Khim. i Tekhnol. Topliv. i Masel* **12**, 27 (1967); *Chem. Abstr.* **67**, 13478 (1967).
- ²¹ C. J. Thompson, H. J. Coleman, R. L. Hopkins, and H. T. Rall, *U.S., Bur. Mines, Rept. Invest.* **6096** (1962); *Chem. Abstr.* **58**, 4353 (1963); *Am. Soc. Testing Mater., Spec. Tech. Publ.* **389**, 329 (1965).

have also been identified in crude petroleum oils.^{16, 24-28} The components of petroleum oil fractions may be partially separated and identified by adsorption and/or GLC techniques. Linear elution adsorption chromatography^{19, 29} and GLC using a microcoulometric sulfur detector¹⁹ have been found to be particularly useful. The identification of benzo[b]thiophenes in the chromatographic fractions usually follows from spectroscopic examination (especially mass spectrometry^{8, 9, 16, 17, 28, 30-32}). The separation by adsorption chromatography of benzo[b]thiophene and a number of other sulfur compounds found in the kerosene fraction of petroleum oil has been studied.³³

The positive identification of the sulfur compounds in crude oils is a difficult problem often complicated by the lack of reference compounds. This difficulty has been overcome by hydrodesulfurization (see Section VIII), which converts the sulfur compounds into known hydrocarbons. Treatment of a petroleum oil fraction with calcium hexamine converts the benzo[b]thiophenes present into aryl mercaptans, which are readily separable from accompanying aromatic hydrocarbons (e.g., naphthalene) and then identified by hydro-

²² C. J. Thompson, H. J. Coleman, C. C. Ward, and H. T. Rall, *Anal. Chem.* **32**, 424 (1960); C. J. Thompson, H. J. Coleman, R. L. Hopkins, and H. T. Rall, *Am. Chem. Soc., Div. Petrol. Chem., Preprints* **10**, C-75 (1965).

²³ M. Pailer and E. Simonitsch, *Monatsh. Chem.* **98**, 1477 (1967).

²⁴ S. F. Birch, *J. Inst. Petrol.* **39**, 185 (1953).

²⁵ S. F. Birch, T. V. Cullum, and R. A. Dean, *Chem. Eng. Data Ser.* **3**, 359 (1958); *Chem. Abstr.* **53**, 17486 (1959).

²⁶ S. F. Birch, T. V. Cullum, R. A. Dean, and R. L. Denyer, *Ind. Eng. Chem.* **47**, 240 (1955).

²⁷ S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.* **20**, 1178 (1955).

²⁸ R. H. Brown and S. Meyerson, *Ind. Eng. Chem.* **44**, 2620 (1952).

²⁹ L. R. Snyder, *Am. Soc. Testing Mater., Spec. Tech. Publ.* **389**, 399 (1965); *Chem. Abstr.* **64**, 13978 (1966).

³⁰ C. J. Thompson, N. G. Foster, H. J. Coleman, and H. T. Rall, *U.S., Bur. Mines, Rept. Invest.* **6879** (1966); *Chem. Abstr.* **66**, 47985 (1967).

³¹ E. J. Gallegos, J. W. Green, L. P. Lindeman, R. L. LeTourneau, and R. M. Teeter, *Anal. Chem.* **39**, 1833 (1967).

³² J. S. Ball and D. S. Rao, *5th Ann. Rept. Res., Petrol. Res. Fund, Am. Chem. Soc.* 131 (1960).

³³ A. T. Svyatoshenko and A. S. Nekrasov, *Dokl. Akad. Nauk SSSR* **97**, 95 (1954); *Chem. Abstr.* **48**, 14171 (1954).

desulfurization to known alkylbenzenes.³⁴⁻³⁶ This method can be used²¹ in conjunction with an ozonolytic analysis of alkylbenzenes reported by Boer.³⁷

Unwanted sulfur-containing components may be removed from petroleum oils by hydrodesulfurization over a Co-Mo catalyst at high temperatures under pressure ("unifining" or "hydrofining").³⁸ However, benzo[b]thiophene is hydrodesulfurized with difficulty over a molybdenum catalyst^{39, 40} and it is difficult to remove completely from petroleum oils by hydrofining.⁴¹

B. IN COAL TAR

The presence of benzo[b]thiophene and two methylbenzo[b]thiophenes in coal tar has been known for some time.⁷ In 1959, 4- and 6-hydroxybenzo[b]thiophene were isolated from the phenolic portions of the washing oil from coal tar.⁴²

Crude naphthalene obtained from coal tar may contain up to 5% benzo[b]thiophene which is only partially removed by selective sulfonation.⁴³⁻⁴⁵ Several improvements⁴⁵⁻⁵¹ make this process more efficient. Other chemical methods of separation include oxidation with peracetic acid, which converts benzo[b]thiophene into its readily separated 1,1-dioxide,⁵² and treatment with ozone, which selectively

³⁴ H. Boer and P. M. Duinker, *Rec. Trav. Chim.* **77**, 346 (1958).

³⁵ J. van Schooten, J. Knotnernus, H. Boer, and P. M. Duinker, *Rec. Trav. Chim.* **77**, 935 (1958).

³⁶ J. Knotnernus, P. M. Duinker, and J. van Schooten, *J. Inst. Petrol.* **47**, 317 (1961).

³⁷ H. Boer, *J. Inst. Petrol.* **46**, 234 (1960).

³⁸ C. H. Watkins and A. J. De Rossett, *Petrol. Refiner* **36**, 201 (1957).

³⁹ M. Yamada, *Kooru Taaru* **12**, 8 (1960); *Chem. Abstr.* **60**, 11978 (1964).

⁴⁰ S. Shono, K. Itabashi, M. Yamada, and M. Kikuchi, *Kogyo Kagaku Zasshi* **64**, 1357 (1961); *Chem. Abstr.* **58**, 4390 (1963).

⁴¹ I. S. Salikhov, R. M. Masagutov, A. Z. Bikkulov, and F. Kh. Urazaev, *Neftepererab. Neftekhim.*, *Akad. Nauk Ukr. SSR, Respub. Mezhd. Sb.* p. 1 (1967); *Chem. Abstr.* **67**, 13530 (1967).

⁴² G. W. Perold and P. F. A. van Lingem, *Chem. Ber.* **92**, 293 (1959).

⁴³ B. M. Pats and A. S. Nepomnyashchaya, *Khim. Prom.* 666 (1959); *Chem. Abstr.* **55**, 960 (1961).

⁴⁴ M. Hřivnáč and J. Janák, *Chem. Průmysl* **10**, 399 (1960); *Chem. Abstr.* **55**, 1299 (1961).

⁴⁵ M. M. Potashnikov, *Koks i Khim.* **31** (1959); *Chem. Abstr.* **54**, 8034 (1960).

⁴⁶ P. P. Karpukhin and A. G. Nikitenko, *Koks i Khim.* **36** (1964); *Chem. Abstr.* **60**, 13066 (1964).

oxidizes the benzo[b]thiophene into easily separated products.⁵³ The purification of naphthalene by heating it with fuller's earth affords 2-(2-naphthyl)benzo[b]thiophene.⁵⁴ A concentrate of 68–74% benzo[b]thiophene is obtained from crude naphthalene by repeated recrystallization of the mixture from methanol containing some phenol, followed by azeotropic distillation of the product with ethylene glycol.⁵⁵ Naphthalene and benzo[b]thiophene are also separable by azeotropic distillation with diethylene glycol or propane-2,3-diol⁵⁶ and by zone refining.⁵⁷ Sublimation of crude naphthalene does not remove any benzo[b]thiophene.⁴⁴ Benzo[b]thiophene in crude naphthalene may be estimated by IR^{58–61} or UV⁵⁹ spectroscopy, by GLC,^{24, 44, 60, 62–64} and by cryoscopic measurements.⁵⁸

- ⁴⁷ T. Ya. Gogoleva and S. S. Boromenskii, *Koks i Khim.* **46** (1964); *Chem. Abstr.* **61**, 495 (1964).
⁴⁸ V. N. Novikov, V. E. Privalov, and V. M. Bednov, *Nauchn. Tr., Vost. Nauchn.-Issled. Uglekhim. Inst.* **16**, 198 (1963); *Chem. Abstr.* **61**, 6823 (1964).
⁴⁹ M. O. Gonzales Garcia, *Rev. Fac. Cienc., Univ. Oviedo [N.S.]* **5**, 143 (1964); *Chem. Abstr.* **62**, 7547 (1965).
⁵⁰ O. Kruber, German Patent 901,177 (1954); *Chem. Abstr.* **53**, 2582 (1959).
⁵¹ A. Schmalenbach, German Patent 945,388 (1956); *Chem. Abstr.* **53**, 698 (1959).
⁵² J. V. Murray and J. R. Anderson, British Patent 761,623 (1956); *Chem. Abstr.* **51**, 8327 (1957); U.S. Patent 2,779,722 (1957); *Chem. Abstr.* **51**, 6128 (1957).
⁵³ M. G. Sturrock and E. L. Cline, U.S. Patent 3,016,401 (1962); *Chem. Abstr.* **56**, 11933 (1962).
⁵⁴ A. H. Lamberton and P. T. McGrail, *Chem. Ind. (London)* 986 (1961); *J. Chem. Soc.* 1776 (1963).
⁵⁵ P. P. Karpukhin and A. G. Nikitenko, *Koks i Khim.* **45** (1964); *Chem. Abstr.* **62**, 3852 (1965).
⁵⁶ J. Gondzik and W. Stateczny, *Przemysl Chem.* **9**, 132 (1953); *Chem. Abstr.* **48**, 11759 (1954).
⁵⁷ A. Aarna and A. Ryatsep, *Tr. Tallinsk. Politekh. Inst.* **A215**, 171 (1964); *Chem. Abstr.* **63**, 17994 (1965).
⁵⁸ S. V. R. Mastrangelo and R. W. Dornte, *Anal. Chem.* **29**, 794 (1957).
⁵⁹ O. Kibino, H. Suzumura, and S. Takeyama, *Kooru Taaru* **12**, 365 (1960); *Chem. Abstr.* **61**, 2883 (1964).
⁶⁰ V. A. Koptug, A. G. Khmel'nitskii, and V. N. Kobrina, *Izv. Sibirsk. Otd. Akad. Nauk SSSR., Ser. Khim. Nauk* 116 (1964); *Chem. Abstr.* **61**, 11813 (1964).
⁶¹ R. E. Seeber and R. G. White, *Anal. Chem.* **31**, 621 (1959).
⁶² A. G. Khmel'nitskii, V. N. Kobrina, and V. A. Koptug, *Koks i Khim.* **44** (1965); *Chem. Abstr.* **63**, 6755 (1965).
⁶³ M. Hrivnác and J. Janák, *Chem. Ind. (London)* 930 (1960).
⁶⁴ G. Schulz, *Z. Anal. Chem.* **181**, 390 (1961).

III. Molecular Structure and Physical Properties of Benzo[*b*]thiophenes

A. MOLECULAR ORBITAL TREATMENT OF BENZO[*b*]THIOPHENE

The molecular orbital treatment of the π system of benzo[*b*]thiophene, like that of thiophene³ and other sulfur heterocycles,⁶⁵ is complicated by the possible involvement of the two $3d$ π orbitals ($3d_{xz}$ and $3d_{yz}$) of the sulfur atom. The model in which the $3d$ π orbitals are fully involved as $3pd^2$ π hybrids (model A),⁶⁶⁻⁶⁸ and the model in which they are not involved at all (model B)^{65, 68-73} can both be made to fit the observed π -electronic properties of benzo[*b*]thiophene by suitable choice of empirical parameters (corresponding to *electropositive* $3pd^2$ π orbitals on model A and *electronegative* $3p$ π orbitals on model B, relative to the carbon $2p$ π orbitals).⁶⁸ In particular, both can account for the order of reactivity of the various positions of benzo[*b*]thiophene toward electrophilic attack, *viz.*, $3 > 2 (> 5)$.⁶⁸ It is clear that a degree less empiricism is needed to distinguish between the two models. The more subtle empiricism of the self-consistent field model B of Momicchioli and Rastelli⁷⁴ and Trinajstić and Hinchliffe,⁷⁵ successful though it may be, does not do this.

Matsuki *et al.* have used the parameters of Kikuchi⁶⁶ to calculate the electron densities at the various positions in some substituted benzo[*b*]thiophenes. Satisfactory correlation with the observed positions of electrophilic substitution is obtained with 5-bromo-⁷⁶ and 2,3-

⁶⁵ R. Zahradník, *Advan. Heterocyclic Chem.* **5**, 1 (1965).

⁶⁶ K. Kikuchi, *Sci. Rept. Tohoku Univ., First Ser.* **41**, 35 (1957); *Chem. Abstr.* **52**, 14317 (1958).

⁶⁷ J. C. Patel, *J. Sci. Ind. Res. (India)* **16B**, 370 (1957).

⁶⁸ R. Zahradník, C. Párkányi, V. Horák, and J. Koutecký, *Collection Czech. Chem. Commun.* **28**, 776 (1963).

⁶⁹ H. Berthod and A. Pullman, *Compt. Rend.*, **C262**, 76 (1966).

⁷⁰ H. François, *Bull. Soc. Chim. France* 515 (1962).

⁷¹ C. Párkányi, V. Horák, J. Pecka, and R. Zahradník, *Collection Czech. Chem. Commun.* **31**, 835 (1966).

⁷² J. Fabian, A. Mehlhorn, and R. Mayer, *Z. Chem.* **5**, 22 (1965).

⁷³ J. Fabian, A. Mehlhorn, J. Bormann, and R. Mayer, *Wiss. Z. Tech. Univ. Dresden* **14**, 285 (1965); *Chem. Abstr.* **64**, 9072 (1966).

⁷⁴ F. Momicchioli and A. Rastelli, *J. Mol. Spectry* **22**, 310 (1967).

⁷⁵ N. Trinajstić and A. Hinchliffe, *Z. Physik. Chem. (Frankfurt)* [N.S.] **59**, 271 (1968).

⁷⁶ Y. Matsuki and F. Shoji, *Nippon Kagaku Zasshi* **86**, 1067 (1965); *Chem. Abstr.* **65**, 13638 (1966).

dibromobenzo[*b*]thiophene,⁷⁷ and 7-methylbenzo[*b*]thiophene-3-carboxaldehyde,⁷⁸ but not with 7-methylbenzo[*b*]thiophene-2-carboxaldehyde.⁷⁸

B. SPECTROSCOPY OF BENZO[*b*]THIOPHENES

1. *NMR Spectra*

The ¹H NMR spectra of some methyl-,⁷⁹⁻⁸³ halo-,⁸¹ mercapto-,⁸⁴ nitro-,⁸⁴ and methoxybenzo[*b*]thiophenes,⁸⁵ and of some sulfonic acids, sulfonyl chlorides, and sulfonate esters⁸⁶ have been recorded. Two groups of workers^{87,88} have independently studied the ¹H NMR spectra of a range of benzo[*b*]thiophene derivatives in an attempt to correlate the chemical shifts of the protons with the substituents. Such a correlation helps to assign structures to new benzo[*b*]thiophene derivatives, and it also throws light on the influence of substituents on the NMR parameters of heteroaromatic systems in general.

The chemical shifts of the six protons in the rather complex ¹H NMR spectrum of benzo[*b*]thiophenes have been estimated from specific deuteration experiments.^{83, 87, 89} The chemical shifts of H-5

⁷⁷ Y. Matsuki and T. Kanda, *Nippon Kagaku Zasshi* **86**, 637 (1965); *Chem. Abstr.* **65**, 674 (1966).

⁷⁸ Y. Matsuki and T.-C. Lee, *Nippon Kagaku Zasshi* **86**, 853 (1965); *Chem. Abstr.* **65**, 13638 (1966).

⁷⁹ K. Takahashi, T. Kanda, and Y. Matsuki, *Bull. Chem. Soc. Japan* **38**, 1799 (1965).

⁸⁰ K. Takahashi, T. Kanda, and Y. Matsuki, *Bull. Chem. Soc. Japan* **37**, 768 (1964).

⁸¹ P. Cagniant, P. Faller, and D. Cagniant, *Bull. Soc. Chim. France* 3055 (1966).

⁸² Y. Matsuki and T. Kanda, *Nippon Kagaku Zasshi* **86**, 643 (1965); *Chem. Abstr.* **65**, 674 (1966).

⁸³ A. S. Angeloni and M. Tramontini, *Boll. Sci. Fac. Chim. Ind. Bologna* **21**, 217 (1963).

⁸⁴ D. E. Boswell, J. A. Brennan, P. S. Landis, and P. G. Rodewald, *J. Heterocyclic Chem.* **5**, 69 (1968).

⁸⁵ A. S. Angeloni and M. Tramontini, *Ann. Chim. (Rome)* **53**, 1740 (1963).

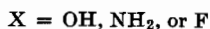
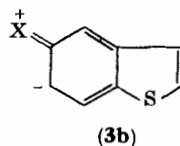
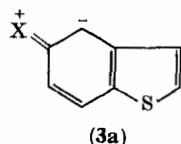
⁸⁶ P. S. Landis, J. A. Brennan, and P. B. Venuto, *J. Chem. Eng. Data* **12**, 610 (1967).

⁸⁷ B. Caddy, M. Martin-Smith, R. K. Norris, S. T. Reid, and S. Sternhell, *Australian J. Chem.* **21**, 1853 (1968).

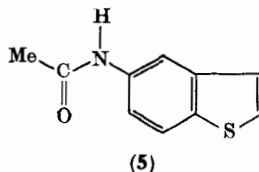
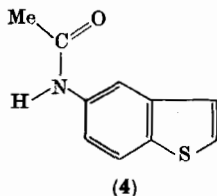
⁸⁸ N. B. Chapman, D. F. Ewing, R. M. Scrowston, and R. Westwood, *J. Chem. Soc., C* 764 (1968).

⁸⁹ K. Takahashi, I. Ito, and Y. Matsuki, *Bull. Chem. Soc. Japan* **39**, 2316 (1966).

and H-6 are approximately the same; that of H-7 is greater than that of H-4, owing to the magnetic anisotropy or electronic effect of the sulfur atom.⁸⁹ In the case of 5-substituted benzo[*b*]thiophenes, a plot of the chemical shifts of the two *ortho* protons (H-4 and H-6) against each other gives a straight line whose slope is not 45°, thereby inferring that H-4 is more susceptible than H-6 to substituent effects from the 5-position.⁸⁷ This is particularly evident when the 5-substituent has a strong mesomeric interaction with the ring in the ground state (+M effect): canonical structure **3a** probably contributes more to the

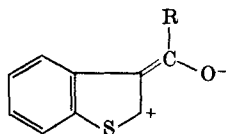


ground state than the higher energy structure **(3b)**.⁸⁸ The abnormally large deshielding of H-4, relative to H-6, in 5-acetamidobenzo[*b*]thiophene⁸⁷ and its 3-methyl derivative⁸⁸ has been discussed in terms of the relative populations of the conformers **(4 and 5)**, using spectra determined over a range of temperatures.⁸⁷

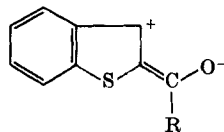


A nitro group causes the adjacent *ortho* protons to move downfield; this shift is useful in making structural assignments.⁸⁴ A 2-ethoxycarbonyl group causes a general deshielding of the benzene ring protons, but the effect is most marked at the 4- and 6-positions, as expected from the mesomeric effect of the substituent.⁸⁸ H-4 of 3-methylbenzo[*b*]thiophene⁸⁸ and H-3 of 4-methylbenzo[*b*]thiophene⁸³ are shielded relative to benzo[*b*]thiophene. In contrast, a methyl substituent in systems containing two fused six-membered rings deshields the *peri* proton. A strongly anisotropic group (e.g., COMe, COEt, CN, CHO) in the 3-position causes a large deshielding of H-4, and allows the proton to be readily identified in the ¹H NMR spectrum.⁸⁸

The shielding of H-2 (*ca.* 40 Hz) by the methyl group in 3-methylbenzo[b]thiophene is much higher than the usual value for aromatic systems (*ca.* 17 Hz), thereby reflecting the high bond order of the 2,3-bond.⁸⁸ A carbonyl group in the 3-position produces a downfield shift of H-2 which is larger than that of H-3 produced by a carbonyl group in the 2-position.^{78, 88, 90} This suggests a greater contribution of structure 6 relative to that of structure 7.⁸⁸



(6)



(7)

The *ortho* coupling constants ($J_{6,7}$) for 5-substituted benzo[b]thiophenes have values similar to the *ortho* coupling constants in benzene derivatives,^{84, 87, 88, 91} and vary directly and linearly with the electronegativity of the 5-substituent.⁸⁷ *Meta* coupling constants vary over the range 1.0–2.5 Hz^{84, 87, 88, 91} and there is no obvious correlation with the electronegativity of the substituent.^{87, 88} $J_{2,3}$ (*ca.* 5.5 Hz)^{79, 83, 84, 86–89, 91–93} is smaller than the benzenoid *ortho* coupling constant and is not markedly affected by substituents in the benzene ring.^{87, 88} The well-established long-range coupling between H-3 and H-7 ($J_{3,7} = 0.6–0.8$ Hz)^{80, 84, 86–89, 94, 95} and H-2 and H-6 ($J_{2,6} = 0.5–0.6$ Hz)^{84, 86–89, 92, 94} in benzo[b]thiophene derivatives is believed to take place along the “straight zigzag” (all-*trans*) conjugated pathways (8) and (9).^{92, 94–96} Smaller long-range coupling (<0.3 Hz) is sometimes observed between H-3 and H-4⁸⁷ and possibly between H-2 and H-4.^{80, 88} Although H-2 and H-5 are connected by a “straight zigzag” pathway, long-range coupling between them has not been observed.⁹⁴

⁹⁰ Y. Matsuki and T.-C. Lee, *Nippon Kagaku Zasshi* **86**, 102 (1965); *Chem. Abstr.* **62**, 16172 (1965).

⁹¹ Y. Matsuki and T.-C. Lee, *Nippon Kagaku Zasshi* **87**, 186 (1966); *Chem. Abstr.* **65**, 15301 (1966).

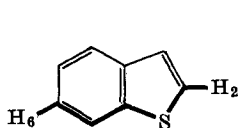
⁹² M. Martin-Smith, S. T. Reid, and S. Sternhell, *Tetrahedron Letters* 2393 (1965).

⁹³ A. Ricci, D. Balucani, and N. P. Buu-Hoi, *J. Chem. Soc., C* 779 (1967).

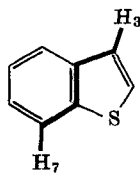
⁹⁴ K. Takahashi, T. Kanda, F. Shoji, and Y. Matsuki, *Bull. Chem. Soc. Japan* **38**, 508 (1965).

⁹⁵ J. A. Elvidge and R. G. Foster, *J. Chem. Soc.* 981 (1964).

⁹⁶ K. Takahashi, *Bull. Chem. Soc. Japan* **39**, 2782 (1966).



(8)



(9)

Benzo[*b*]thiophenes containing a methyl substituent in the benzene ring show coupling of the methyl protons with an adjacent ring proton (*ortho* side-chain coupling; $J = 0.6\text{--}0.7$ Hz),^{79, 88, 90} and a much smaller coupling with other ring protons.⁷⁹ Much larger splittings are observed between H-3 and a 2-methyl group ($J_{2',3} = 0.8\text{--}1.0$ Hz)^{79, 83, 97} and between H-2 and a 3-methyl group ($J_{2,3'} = 1.1\text{--}1.5$ Hz),^{79, 83, 88, 95, 97} owing to the more localized nature of the 2,3-double bond. A similar effect is observed in the case of mercaptobenzo[*b*]thiophenes: $J_{\text{SH}-o-\text{H}}$ is *ca.* 0.2 Hz when the mercapto group is substituted in the benzene ring, but rises to 1.3 Hz when it is substituted in the thiophene ring.⁸⁴ The trifluoromethyl group in 3-methyl-5-trifluoromethylbenzo[*b*]thiophene shows substantial coupling, not only with the adjacent ring protons ($J_{4,\text{CF}_3} = 0.7$ Hz), but also with H-7 ($J_{7,\text{CF}_3} = 0.7$ Hz).⁸⁸ 2,3-Dimethylbenzo[*b*]thiophene shows homobenzylic coupling ($J_{2',3'} = 0.75$ ⁷⁹ or 0.8 Hz⁸⁸).

The ¹H NMR spectra of several benzo[*b*]thiophene-1,1-dioxides show the following features (relative to the unoxidized benzo[*b*]thiophenes): H-2 and H-4 are consistently shielded, H-5 and H-6 are consistently deshielded, H-3 is little affected, and the changes in H-7 are small and of variable sign.⁸⁸ The loss of aromaticity of the thiophene ring on oxidation of the sulfur atom leads to a more localized 2,3-double bond, and a consequent increase in $J_{2,3}$, $J_{2,3'}$, and $J_{2',3}$ (primes denote coupling to protons on a methyl group attached to the position numbered). $J_{2,6}$ is no longer observed, since the conjugated pathway (8) over which this coupling operates is partially removed by oxidation of the sulfur atom.⁸⁸

The versatility of the NMR method for determining the position of substituents in the benzo[*b*]thiophene nucleus is becoming increasingly recognized. It is relatively easy to locate directly a single substituent in either the 5- or 6-position, or in the 4- or 7-position, but a more precise location requires further information such as the long-range

⁹⁷ S. H. Groen, R. M. Kellogg, J. Buter, and H. Wynberg, *J. Org. Chem.* **33**, 2218 (1968).

coupling constants, $J_{2,6}$ and $J_{3,7}$.^{76-78,82,91,98,99} This method is of particular value for nitrobenzo[*b*]thiophenes in which the long-range coupling constants are readily measured.^{84,99} The products obtained from the nitration,⁹⁹⁻¹⁰¹ bromination,^{76,78,81,90,91} and acetylation^{76,77,82,98,102,103} of several benzo[*b*]thiophene derivatives have been identified by the above methods.

When a cyclization reaction leads to mixtures of two isomeric benzo[*b*]thiophenes, their relative proportions are readily estimated by examination of the ¹H NMR spectrum of the mixture.^{95,104-106} Mixtures obtained by acetylation⁹⁸ and bromination^{76,90} reactions and by Baeyer-Villiger oxidation of acetylbenzo[*b*]thiophenes¹⁰⁷ have been similarly analyzed. The ¹⁹F NMR spectra of several polyfluorobenzo[*b*]thiophenes have been examined,^{103,108-111} and used to study the reaction of 4,5,6,7-tetrafluorobenzo[*b*]thiophene with nucleophiles.¹⁰³ The tautomerism of 2-amino-,¹¹²⁻¹¹⁴ 3-*N*-phenylamino-,¹¹⁵ and 3-hydroxybenzo[*b*]thiophene^{109,115-117} derivatives has been studied by ¹H NMR spectroscopy.

⁹⁸ Y. Matsuki and T. Kanda, *Nippon Kagaku Zasshi* **86**, 99 (1965); *Chem. Abstr.* **62**, 16172 (1965).

⁹⁹ K. J. Armstrong and M. Martin-Smith, *London Chem. Soc., Heterocyclic Group Meeting, Salford*, 1968; *Quart. Repts. Sulfur Chem.* **3**, 357 (1968).

¹⁰⁰ F. G. Bordwell and T. W. Cutshall, *J. Org. Chem.* **29**, 2020 (1964).

¹⁰¹ R. Westwood, Ph.D. Thesis, *University of Hull* (1967).

¹⁰² Y. Matsuki and I. Ito, *Nippon Kagaku Zasshi* **88**, 751 (1967); *Chem. Abstr.* **69**, 18961 (1968).

¹⁰³ G. M. Brooke and M. A. Quasem, *Tetrahedron Letters* 2507 (1967).

¹⁰⁴ P. Cagniant and D. Cagniant, *Bull. Soc. Chim. France* 3674 (1966).

¹⁰⁵ Y. Matsuki and I. Ito, *Nippon Kagaku Zasshi* **88**, 758 (1967); *Chem. Abstr.* **69**, 59018 (1968).

¹⁰⁶ Y. Matsuki and F. Shoji, *Nippon Kagaku Zasshi* **88**, 755 (1967); *Chem. Abstr.* **69**, 59020 (1968).

¹⁰⁷ Y. Matsuki and K. Fujieda, *Nippon Kagaku Zasshi* **88**, 1193 (1967); *Chem. Abstr.* **69**, 51921 (1968).

¹⁰⁸ G. M. Brooke, *Tetrahedron Letters* 4049 (1968).

¹⁰⁹ G. M. Brooke and M. A. Quasem, *J. Chem. Soc., C* 865 (1967).

¹¹⁰ M. D. Castle, R. G. Plevvey, and J. C. Tatlow, *J. Chem. Soc., C* 1225 (1968).

¹¹¹ M. D. Castle, E. F. Mooney, and R. G. Plevvey, *Tetrahedron* **24**, 5457 (1968).

¹¹² G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *J. Org. Chem.* **30**, 4074 (1965).

¹¹³ G. W. Stacy and T. E. Wollner, *J. Org. Chem.* **32**, 3028 (1967).

¹¹⁴ K. Gewald and G. Neumann, *Chem. Ber.* **101**, 1933 (1968).

¹¹⁵ N. P. Buu-Hoi, V. Bellavita, A. Ricci, and G. Grandolini, *Bull. Soc. Chim. France* 2658 (1965).

¹¹⁶ H. J. Jakobsen and S.-O. Lawesson, *Tetrahedron* **21**, 3331 (1965).

¹¹⁷ M. S. El Shanta, R. M. Scrowston, and M. V. Twigg, *J. Chem. Soc., C* 2364 (1967).

An NMR method has been used to determine the association constant of benzo[*b*]thiophene with the electron acceptors 1,4-dinitrobenzene and 1,3,5-trinitrobenzene in chloroform solution.¹¹⁸ The ¹H NMR spectra of some sulfur analogs of cholanthrene and methylcholanthrene have been analyzed.¹¹⁹

2. Mass Spectra

The mass spectra of benzo[*b*]thiophene and several of its derivatives have been recorded,¹²⁰⁻¹²⁴ but only two systematic analyses of such spectra have been made.^{121, 123} The relatively high stability of benzo[*b*]thiophene to electron impact^{120, 125} has been compared with that of other heterocyclic and aromatic systems.¹²⁵

The main features of the mass spectrum of benzo[*b*]thiophene have been established by Porter,¹²¹ using the spectrum of 3-deutero-benzo[*b*]thiophene for comparison purposes. Triply charged ions have been detected in the mass spectra of benzo[*b*]thiophene and its 2- and 3-methyl derivatives.¹²⁶

The mass spectra of 2- and 3-methylbenzo[*b*]thiophene are almost identical,¹²¹ because in each case the loss of one hydrogen atom leads to the same benzothiopyrylium cation (**11**) as base peak.^{121, 123, 124} The mass spectra of the two compounds may then be rationalized in terms of further decomposition of (**11**).¹²¹ The sole difference in the spectra of 2- and 3-methylbenzo[*b*]thiophene is the presence of the weak ion Me—C≡S⁺ in the former, formed by extrusion of C-2 and its attached sulfur atom and methyl group.¹²¹

The base peak in the spectra of 2-ethyl- and 2-*n*-propylbenzo[*b*]thiophene (**10**; R=Me or Et, respectively) and their derivatives

¹¹⁸ R. Foster and C. A. Fyfe, *J. Chem. Soc.*, B 926 (1966).

¹¹⁹ P. Faller, *Bull. Soc. Chim. France* 387 (1967).

¹²⁰ W. E. Haines, R. V. Helm, G. L. Cook, and J. S. Ball, *Am. Chem. Soc., Div. Petrol. Chem., Gen. Papers* **33**, 209 (1955); *Chem. Abstr.* **50**, 13004 (1956).

¹²¹ Q. N. Porter, *Australian J. Chem.* **20**, 103 (1967).

¹²² "Catalog of Mass Spectral Data," Am. Petrol. Inst., Res. Project No. 44. Carnegie Inst., Technol., Pittsburgh, Pennsylvania.

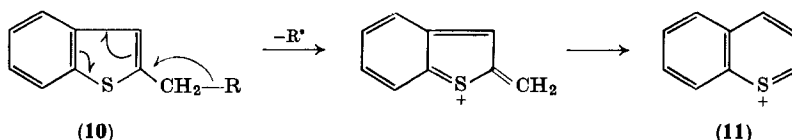
¹²³ H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," p. 631. Holden-Day, San Francisco, California, 1967.

¹²⁴ G. L. Cook and N. G. Foster, *Proc. Am. Petrol. Inst., Sect. III* **41**, 199 (1961).

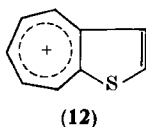
¹²⁵ J. E. Collin, *Bull. Soc. Chim. Belges* **72**, 38 (1963).

¹²⁶ S. Meyerson and R. W. V. Haar, *J. Chem. Phys.* **37**, 2458 (1962).

results from β -cleavage with loss of a methyl or ethyl group, respectively, and formation of the benzothiopyrylium ion (11).^{121, 123}



The mass spectra of 4-, 5-, and 7-methylbenzo[b]thiophene are almost identical, strongly suggesting that in each case the loss of a hydrogen atom from the molecular ion leads to the thienotropylium ion (12).¹²¹



The mass spectra of 2-phenyl-, 3-phenyl-, and 3-methyl-2-phenylbenzo[b]thiophene have been discussed, and tentative structural assignments of the main fragment ions have been made.¹²¹ The mass spectra of benzo[b]thiophene-1,1-dioxide and its 2,3-dihydro derivative have been examined in detail.^{121, 127} The partial mass spectrum of 2,3-dihydrobenzo[b]thiophene has been recorded.¹²⁴

3. IR Spectra

Several workers^{120, 128-131} have recorded the IR spectrum of benzo[b]thiophene, but the assignment of bands is far from complete. The CH out-of-plane bending (γ -CH) frequencies of the benzene ring, which occur in the region 967-758 cm^{-1} , have been most fully examined.¹²⁸

The IR spectra of many substituted benzo[b]thiophenes have been examined in an effort to correlate band positions with the substitution

¹²⁷ J. Heiss, K.-P. Zeller, and B. Zeeh, *Tetrahedron* **24**, 3255 (1968).

¹²⁸ J. Derkosch and I. Specht, *Mikrochim. Acta* **55** (1962).

¹²⁹ D. G. O'Sullivan, *J. Chem. Soc.* 3278 (1960).

¹³⁰ W. E. Haines, R. V. Helm, G. L. Cook, and J. S. Ball, *J. Phys. Chem.* **60**, 549 (1956).

¹³¹ V. T. Aleksanyan, Ya. M. Kumel'fel'd, S. M. Shostakovskii, and A. I. L'vov, *Zh. Prikl. Spektroskopii, Akad. Nauk Belorussk. SSSR* **3**, 355 (1965); *Chem. Abstr.* **64**, 10613 (1966).

pattern.^{81, 104, 128, 132-139} Bellamy's¹⁴⁰ correlations between γ -CH frequencies and substitution pattern in the benzene series can be slightly modified and applied fairly successfully to substituted benzo[*b*]thiophenes.¹³³ Benzo[*b*]thiophenes which are unsubstituted in the benzene ring can readily be identified by the presence of a strong band in each of the regions 770-755 and 735-725 cm^{-1} ,¹³³ and by a characteristic low intensity quintet in the region 1945-1785 cm^{-1} .¹²⁸ It is relatively easy to distinguish by means of the γ -CH modes between a single substituent in the 5- or 6-position, on the one hand, and in the 4- or 7-position, on the other hand, but further distinction is not easy.^{128, 133} Derkosch and Specht¹²⁸ claim that benzo[*b*]thiophenes with no substituents in the heterocyclic ring give rise to a band at 690-680 cm^{-1} , but this has not always been observed by other workers.¹³³ This band sometimes appears in the same position in the spectra of 2- or 3-monosubstituted, or 2,3-disubstituted benzo[*b*]thiophenes,¹³³ but is sometimes 15 cm^{-1} higher.¹²⁸ Contrary to earlier claims,^{134, 135} it is not possible to distinguish with certainty between 2- and 3-substituted benzo[*b*]thiophenes by IR spectroscopy.¹³³ It is possible to identify the isomeric mononitrobenzo[*b*]thiophenes⁸⁴ and their 2-formyl derivatives^{141, 142} by their IR spectra and to distinguish between certain 3,4-disubstituted benzo[*b*]thiophenes and their 3,6-disubstituted isomers.¹⁴³

The C=O absorption band of several 2-benzo[*b*]thienyl ketones is stated to occur at a frequency lower than that of the corresponding

¹³² R. Royer, P. Demerseman, and A. Cheutin, *Bull. Soc. Chim. France* 1534 (1961).

¹³³ A. Cheutin, M.-L. Desvoye, R. Royer, P. Demerseman, and J.-P. Lechartier, *Compt. Rend.* **261**, 705 (1965).

¹³⁴ D. Cagniant, P. Faller, and P. Cagniant, *Bull. Soc. Chim. France* 2410 (1961).

¹³⁵ D. Cagniant, P. Cagniant, and P. Faller, *Bull. Soc. Chim. France* 576 (1962).

¹³⁶ P. Cagniant, P. Faller, and D. Cagniant, *Bull. Soc. Chim. France* 1525 (1964).

¹³⁷ P. Cagniant, D. Cagniant, and P. Faller, *Bull. Soc. Chim. France* 1756 (1964).

¹³⁸ P. Cagniant, D. Cagniant, and M. Mennrath, *Bull. Soc. Chim. France* 1765 (1964).

¹³⁹ P. Cagniant, P. Faller, and D. Cagniant, *Bull. Soc. Chim. France* 2423 (1964).

¹⁴⁰ L. J. Bellamy, "The Infrared Spectra of Complex Molecules," p. 65. Methuen, London, 1958.

¹⁴¹ V. P. Mamaev and O. P. Shkurko, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* 516 (1965); *Chem. Abstr.* **64**, 675 (1966).

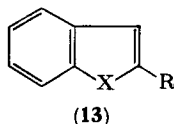
¹⁴² V. P. Mamaev and O. P. Shkurko, *Sb. Dokl. Sib. Soveshch. Spektrosk., 3rd, Krasnoyarsk, USSR*, 1964 45 (1966); *Chem. Abstr.* **68**, 68250 (1968).

¹⁴³ R. D. Schuetz and R. L. Titus, *J. Heterocyclic Chem.* **4**, 465 (1967).

3-isomer,^{71, 132, 144} as expected in view of the increased conjugation of the carbonyl group in the 2-position over that in the 3-position. However, Derkosch and Specht have reported¹²⁸ that the position of the C=O band is independent of the position of the C=O group on the thiophene ring.

In view of the existing confusion on the IR spectroscopy of benzo[b]-thiophenes, it is evident that problems of orientation are best approached by the joint application of IR and other spectroscopic techniques.

In the series **13** (R = H or Me, X = O, NR, S, or Se), the γ -CH frequencies increase linearly with increasing electronegativity of the heteroatom X.¹⁴⁵ Intensity measurements on the ν -CH bands of compounds in series **13** (R = H, X = O, NR, or S) indicate their dependence on the electronegativity of the heteroatom, the degree of hybridization of the CH orbitals, and the consequent variation in charge distribution in the molecule.¹⁴⁶



IR spectroscopy has been used to show that 2-aminobenzo[b]thiophenes normally exist solely as the amino tautomer,¹¹²⁻¹¹⁴ and that 2-^{112, 113} and 3-hydroxybenzo[b]thiophenes^{117, 147} exist solely as the keto tautomers, except that compounds with an adjacent carbonyl-containing group exist mainly as the enols.^{109, 116, 147, 148} 3-Hydroxy-2-nitrobenzo[b]thiophene-1,1-dioxide exists as a mixture of the keto and enol forms.¹⁴⁹

Martin-Smith *et al.*^{150, 151} have studied hydrogen bonding in several

¹⁴⁴ M. S. El Shanta and R. M. Scowston, *J. Chem. Soc., C* 2084 (1967).

¹⁴⁵ P. Bassignana, C. Cogrossi, and M. Gandino, *Chim. Ind. (Paris)* **90**, 370 (1963).

¹⁴⁶ R. Joeckle, E. Lemperle, and R. Meeke, *Z. Naturforsch.* **22a**, 395 (1967).

¹⁴⁷ T. P. C. Mulholland, R. I. W. Honeywood, H. D. Preston, and D. T. Rosevear, *J. Chem. Soc.* 4939 (1965).

¹⁴⁸ N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Lepley, *J. Org. Chem.* **32**, 2678 (1967).

¹⁴⁹ M. A. Matskanova and A. Arens, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* 362 (1966); *Chem. Abstr.* **65**, 15193 (1966).

¹⁵⁰ I. Brown, G. Eglinton, and M. Martin-Smith, *J. Chem. Soc.* 2551 (1963).

¹⁵¹ I. Brown, G. Eglinton, and M. Martin-Smith, *Spectrochim. Acta* **18**, 1593 (1962).

substituted 5-hydroxybenzo[*b*]thiophenes by IR spectroscopy. Solutions of 3-methoxycarbonyl-, 3-cyano-, 3-nitro-, or 3-acetyl-5-hydroxybenzo[*b*]thiophene contain hydrogen-bonded dimers.¹⁵⁰ In the case of 4-bromo-5-hydroxy-3-nitrobenzo[*b*]thiophene, only the intermolecular OH...Br bond is observed at the concentration examined.^{150, 151} This compound may be distinguished from its 6-nitro isomer by the position of its OH stretching frequency.¹⁵²

The IR spectra of *cis*- and *trans*-octahydrobenzo[*b*]thiophene have been recorded.²⁷ IR data have been given for several benzo[*b*]thiophene sulfonic acids and their derivatives.⁸⁶

The loss of aromaticity of the thiophene ring in benzo[*b*]thiophene-1,1-dioxides is reflected in their IR spectra.¹³¹ Substituted benzo[*b*]thiophene-1,1-dioxides generally show a very strong single absorption band at *ca.* 1300 cm⁻¹ (asym. $\nu_{S=O}$)¹⁵³ and a strong threefold absorption (thought to arise from Fermi resonance with lower frequency S=O vibrations) in the usual region of the symmetric S=O stretching vibration for sulfones.¹⁵⁴ The separation and exact frequencies of the three bands vary widely with the nature and positions of the substituent groups.¹⁵⁴

4. UV Spectra

The UV spectrum of benzo[*b*]thiophene has been obtained in solution^{120, 130, 134, 155-167} and in the vapor phase,¹⁶⁸⁻¹⁷² mainly for

¹⁵² M. Martin-Smith and S. T. Reid, *J. Chem. Soc.* 938 (1960).

¹⁵³ P. M. G. Bavin, G. W. Gray, and A. Stephenson, *Spectrochim. Acta* **16**, 1312 (1960).

¹⁵⁴ G. Collier and R. M. Scrowston, unpublished work (1968).

¹⁵⁵ R. D. Obolentsev and N. S. Lyubopytova, *Khim. Seraorgan. Soedin., Soderzhashch. v Neft. i Nefteprod., Akad. Nauk SSSR, Bashkirsk. Filial* **7**, 281 (1964); *Chem. Abstr.* **63**, 3783 (1965).

¹⁵⁶ A. I. Kiss, *Acta Univ. Szeged., Acta Phys. Chem. [N.S.]* **5**, 45 (1959); *Chem. Abstr.* **55**, 13037 (1961).

¹⁵⁷ A. I. Kiss and B. R. Muth, *Acta Chim. Acad. Sci. Hung.* **11**, 365 (1957); *Chem. Abstr.* **51**, 15271 (1957).

¹⁵⁸ G. M. Badger and B. J. Christie, *J. Chem. Soc.* 3438 (1956).

¹⁵⁹ M. R. Padhye and S. R. Desai, *Trans. Faraday Soc.* **49**, 1386 (1953).

¹⁶⁰ R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," Fig. 6. Wiley, New York, 1951.

¹⁶¹ P. Ramart-Lucas and M. Martynoff, *Compt. Rend.* **236**, 2247 (1953).

¹⁶² A. S. Angeloni and M. Tramontini, *Ann. Chim. (Rome)* **53**, 1665 (1963).

¹⁶³ M. R. Padhye and J. C. Patel, *J. Sci. Ind. Res. (India)* **15B**, 171 (1956).

¹⁶⁴ R. D. Schuetz and L. Ciporin, *J. Org. Chem.* **23**, 209 (1958).

comparison with the spectra of the π -isoelectronic systems, naphthalene,^{156-159, 168, 169} benzo[b]selenophene,^{156, 157, 163, 171} indole, and benzofuran.^{156, 158, 171, 172} In ethanolic solution it shows three well-defined zones of absorption: (A) a very intense band at 227.5 m μ ; (B) a central zone at 249-262 m μ , characterized by a maximum preceded and followed by two inflections; and (C) a series of bands between 281 and 297 m μ .¹⁶² Zone C is very much more intense in benzo[b]thiophene than in naphthalene, otherwise the spectra are closely similar.^{158, 159} There is a pronounced bathochromic shift of the zone-A band along the series benzofuran, indole, benzo[b]thiophene, and benzo[b]selenophene.^{156, 158} A partial vibrational analysis has been made of the near-UV spectrum of gaseous benzo[b]thiophene.¹⁶⁸⁻¹⁷²

The solvent perturbation technique has been used to study the absorption bands attributable to singlet-triplet transitions in benzo[b]thiophene, using ethyl iodide as the perturbing solvent.¹⁷³ Attempts to obtain information on the π -electron conjugation in the 5-membered ring of benzo[b]thiophene by examination of the vibrational structure of the electronic spectrum were unsuccessful.¹⁷¹ UV evidence suggests that the valence shell of the sulfur atom can expand to a 10-electron structure in benzo[b]thiophene.¹⁵⁶

The UV spectra of benzo[b]thiophene-1,1-dioxides, in which the aromaticity of the thiophene ring is lost, or at least partially lost,¹⁵⁸ generally show only two zones of absorption.^{107, 154, 174} The zone-C bands of the parent compound often remain unchanged in position and intensity, and an intense broad band (often showing fine structure) appears in the region 220-250 m μ .

¹⁶⁵ R. J. Collins and E. V. Brown, *J. Am. Chem. Soc.* **79**, 1103 (1957).

¹⁶⁶ O. P. Kharitonova, *Opt. i Spektroskopiya*, *Akad. Nauk SSSR, Otd. Fiz.-Mat. Nauk, Sb. Statei* **1**, 77 (1963); *Chem. Abstr.* **59**, 5904 (1963).

¹⁶⁷ R. D. Obolentsev and N. S. Lyubopytova, *Khim. Ser-Organ. Soedin., Soderzhashch. v Neft. i Nefteprod., Akad. Nauk SSSR, Bashkirsk. Filial., Materialy Z-oi [Vtoroi] Nauchn. Sessii Ufa*, 1956 105 (1958); *Chem. Abstr.* **53**, 12828 (1959).

¹⁶⁸ M. R. Padhye and J. C. Patel, *Trans. Faraday Soc.* **49**, 1119 (1953).

¹⁶⁹ O. P. Kharitonova, *Opt. i Spektroskopiya* **14**, 214 (1963); *Chem. Abstr.* **58**, 13300 (1963).

¹⁷⁰ R. C. Heckman and H. Sponer, *Phys. Rev.* **91**, 242 (1953).

¹⁷¹ J. M. Hollas, *Spectrochim. Acta* **19**, 753 (1963).

¹⁷² G. Vishwanath, *Current Sci. (India)* **22**, 141 (1954).

¹⁷³ M. R. Padhye and J. C. Patel, *J. Sci. Ind. Res. (India)* **15B**, 206 (1956).

¹⁷⁴ O. Dann and P. Nickel, *Ann. Chem.* **667**, 101 (1963).

TABLE I
UV SPECTRAL DATA FOR SOME MONOSUBSTITUTED BENZO[*b*]THIOPHENES

Substituents	[λ_{\max} (m μ) (log ϵ)]			Ref.
	Zone A	Zone B	Zone C	
H ^a	226 (4.4)	248 (3.7), 257 (3.8), 265 (3.62)	289 (3.22), 296 (3.5)	159
2-Me ^b	229.5 (4.47)	259.5 (3.89)	288 (3.27), 297.5 (3.34)	182
3-Me ^c	232.5 (4.42)	262.5 (3.66)	291 (3.44), 299.5 (3.54)	162
5-Me ^a	230 (4.35)	258 (3.97), 266 (3.67)	291 (3.25), 303 (3.34)	159
6-Me ^a	228 (4.48)	260 (3.83), 266 (3.79)	291 (3.33), 300 (3.19)	159
7-Me ^a	225 (4.39)	257 (3.87), 265 (3.80)	290 (3.43), 300 (3.57)	159
5-Cl ^a	229 (4.49)	262 (3.75), 271 (3.36)	296 (3.25), 306 (3.35)	159
6-Cl ^a	228 (4.49)	263 (3.83), 271 (3.81)	293 (3.41), 303 (3.5)	159
7-Cl ^a	225 (4.46)	259 (3.78), 267 (3.71)	293 (3.53), 302 (3.57)	159
5-OMe ^a	236 (4.31)	259 (3.83), 267 (3.78)	300 (3.43), 306 (3.43), 312 (3.48)	159
6-OMe ^a	230 (4.47)	264 (3.90), 272 (3.86)	294 (3.09), 302 (3.04), 306 (3.11)	159
7-OMe ^a	222 (4.51)	256 (3.83), 264 (3.76)	295 (3.65), 302 (3.56), 306 (3.73)	159
3-NO ₂ ^e	216.5 (4.51)	242 (4.03), 249 (3.98)	326 (3.79)	162
4-NO ₂ ^e	211.5 (4.24)	252 (4.19), 257.5 (4.18)	342 (3.78)	162
5-NO ₂ ^e	—	248 (4.31), 263.5 (4.35)	302.5 (3.68)	162
2-Ph ^e	232 (4.32)	254 (4.09)	297 (4.38)	185
3-Ph ^e	231 (4.39)	263 (3.83)	293 (3.63), 302 (3.64)	185
2-CO ₂ H ^e	229 (4.26)	276 (4.20)	310 (3.56)	339
3-CO ₂ H ^e	213 (4.55)	279 (3.73)	300 (3.76)	91
2-CHO ^d	232 (4.19)	245 (3.85)	297 (4.26)	91
3-CHO ^d	217 (4.55)	239 (4.02)	302 (3.90)	91
2-COMe ^e	232 (4.16)	247 (3.92)	296 (4.25)	423
3-COMe ^e	219 (4.57)	240 (4.01)	303 (3.90)	423

^a In *n*-hexane.^b In heptane.^c In cyclohexane.^d In methanol.^e In ethanol.

A molecular orbital treatment of the UV spectrum of benzo[b]thiophene has been given.^{68, 72, 74, 75} The luminescence^{166, 175} and phosphorescence^{176, 177} spectra of benzo[b]thiophene have been recorded; its singlet-triplet absorption spectrum has been measured.¹⁷⁸

Prominent bands in the vapor phase UV spectra of 3-chloro-,¹⁷⁹ 5-chloro-,^{180, 181} and 7-bromobenzo[b]thiophene¹⁸¹ have been tentatively assigned. Spectra of substituted benzo[b]thiophenes in various solvents have been recorded but not examined in detail; data for a number of monosubstituted derivatives have been collected in Table I.

Attempts to correlate the position of the substituent with the UV spectrum have been largely unsuccessful, but some general comments may be made. The spectra of most monosubstituted derivatives resemble that of benzo[b]thiophene and the three distinct zones usually remain. Methyl or halo substituents cause an overall bathochromic shift relative to benzo[b]thiophene—zone B is most affected by 3-, 5-, or 6-substituents; zone C by 5-substituents.^{134, 159, 162} 3-Alkylbenzo[b]thiophenes are characterized by zone-B bands of lower intensity than those of benzo[b]thiophene and its other alkyl derivatives.¹³⁴ The UV spectra of 2-methylbenzo[b]thiophene and its selenium analog have been compared.¹⁸²

The maximum bathochromic shift of the zone B bands of methoxybenzo[b]thiophenes occurs with the 6-substituted compound; a hypsochromic shift of the A and B bands is observed for 7-methoxybenzo[b]thiophene.^{85, 159}

The inductive and mesomeric effect of the nitro group causes considerable shifts in the spectra of nitrobenzo[b]thiophenes. The zone-A bands are shifted to lower wavelength and may not be observed at all; the zone-C bands are shifted strongly toward the red and appear as an

¹⁷⁵ M. T. Shpak and N. I. Sheremet, *Opt. i Spektroskopiya, Akad. Nauk SSSR, Otd. Fiz.-Mat. Nauk, Sb. Statei* **1**, 110 (1963); *Chem. Abstr.* **59**, 7058 (1963).

¹⁷⁶ Y. Kanda, R. Shimada, Y. Gondo, M. Nakamizo, K. Hanada, M. Koyanagi, and Y. Takenoshita, *Proc. Intern. Symp. Mol. Struct. Spectry., Tokyo*, 1962 **B 303. Sci. Council Japan, Tokyo**, 1963; *Chem. Abstr.* **61**, 1406 (1964).

¹⁷⁷ R. C. Heckman, *J. Mol. Spectry* **2**, 27 (1958).

¹⁷⁸ D. F. Evans, *J. Chem. Soc.* 2753 (1959).

¹⁷⁹ K. Sreeramamurty and P. B. V. Haranath, *Proc. Natl. Inst. Sci. India* **A20**, 318 (1954).

¹⁸⁰ K. Sreeramamurty and P. B. V. Haranath, *Current Sci. (India)* **22**, 296 (1953).

¹⁸¹ M. R. Padhye and R. P. Punyarthi, *Proc. Indian Acad. Sci.* **A48**, 130 (1958).

¹⁸² B. R. Muth and A. I. Kiss, *J. Org. Chem.* **21**, 576 (1956).

intense broad band.¹⁶² The latter effect is most marked in the 2- and 4-nitro derivatives.¹⁶² The UV spectra of 5- and 6-monosubstituted derivatives reveal that the 5- and 6-positions, each of which corresponds to a β -position in naphthalene, are not equivalent, probably owing to the inductive effect of the electronegative sulfur atom.¹⁵⁹

Matsuki and Lee⁹¹ have listed the UV spectra of all the isomeric benzo[*b*]thiophene aldehydes and carboxylic acids. The spectra of the 4- and 7-substituted compounds of each series are very similar. Compounds containing a carbonyl group at the 2-position show a very large bathochromic shift of the A band compared with the corresponding 3-isomer.^{91, 183} Similar behavior is observed in the thiophene series,³ and indicates a greater conjugation of the 2- than of the 3-carbonyl group with the ring. The oxime and semicarbazone of 2-acetylbenzo[*b*]thiophene both show UV absorption similar to that of the parent ketone. The spectra of the corresponding derivatives of 2-benzo[*b*]thienyl *tert*-butyl ketone lack the high intensity absorption of the parent ketone and resemble closely the spectrum of benzo[*b*]thiophene; this has been attributed to steric inhibition of resonance by the *tert*-butyl group.^{161, 184}

The UV spectrum of 3-phenylbenzo[*b*]thiophene^{185, 186} resembles that of benzo[*b*]thiophene, since steric interaction between the *ortho* hydrogens of the phenyl group and H-4 prevents complete conjugation. Such steric effects are absent from 2-phenylbenzo[*b*]thiophene, and its spectrum is widely different from that of the parent.^{174, 185}

Attempts to correlate structure and spectra in the case of di- and polysubstituted compounds have again been largely unsuccessful. The spectra of various dialkylbenzo[*b*]thiophenes are very similar to those of monoalkyl derivatives, except that the bathochromic shift relative to benzo[*b*]thiophene is more pronounced.^{104, 134, 187} It is claimed that the sharp peaks in the 290–305 $m\mu$ region of the spectra of 5-substituted 2,3-dialkylbenzo[*b*]thiophenes are replaced by points of inflection in similar 6-substituted compounds, allowing such isomers to be distinguished.^{81, 104, 136} Several 2-acetyl- and 3-acetyl-

¹⁸³ Y. Matsuki and Y. Adachi, *Nippon Kagaku Zasshi* **89**, 192 (1968); *Chem. Abstr.* **69**, 67165 (1968).

¹⁸⁴ P. Ramart-Lucas, *Bull. Soc. Chim. France* 1017 (1954).

¹⁸⁵ S. Middleton, *Australian J. Chem.* **12**, 218 (1959).

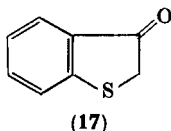
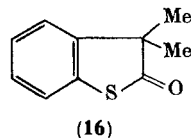
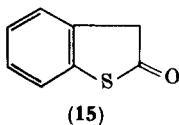
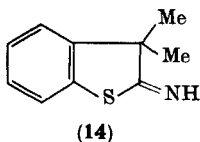
¹⁸⁶ D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res. (India)* **18B**, 77 (1959).

¹⁸⁷ E. G. G. Werner, *Rec. Trav. Chim.* **68**, 509 (1949).

methylbenzo[b]thiophenes have been distinguished by the lack of bands in the 250–260 $m\mu$ region of the spectrum of the 3-acetyl derivative.⁹⁸ UV data have been given for the following disubstituted compounds: 2- and 3-substituted 5-bromobenzo[b]thiophenes,⁷⁶ all the isomeric 3-bromobenzo[b]thiophene aldehydes,⁹¹ several isomeric nitrobenzo[b]thiophene-2-carboxaldehydes,^{141, 142} 2-⁹⁰ and 3-substituted⁷⁸ 7-methylbenzo[b]thiophenes, 6-substituted 3-bromobenzo[b]thiophenes,⁷⁷ 4-, 5-, 6-, and 7-bromo-3-methylbenzo[b]thiophene,¹⁰⁵ and various bromo-substituted methylbenzo[b]thiophenes and their 1,1-dioxides.¹⁰⁶

UV spectra of tri-,^{104, 134, 136, 139, 187} tetra-,^{81, 134, 136, 139, 187, 188} and pentaalkylbenzo[b]thiophenes¹³⁹ and of several of their monohalo derivatives⁸¹ have been recorded. Spectra have been given for substituted dimethoxy-¹⁸⁹ and 5,6-methylenedioxybenzo[b]thiophenes,^{189, 190} and 6-substituted 2,3-dibromobenzo[b]thiophenes.⁷⁷

The UV spectrum of 3,3-dimethyl-2-imino-2,3-dihydrobenzo[b]thiophene (**14**) is quite similar to that of 2,3-dihydrobenzo[b]thiophene.¹¹³ On the other hand, the spectrum of 2-aminobenzo[b]thiophene diverges from that of **14**, but closely matches that of benzo[b]thiophene. 2-Aminobenzo[b]thiophene exists, therefore, mainly as the amino tautomer.^{112–114} On the contrary, thiooxindole (**15**) exists in solution mainly as the oxo form since its spectrum closely resembles that of the thiolactone (**16**) and the imine (**14**).¹¹³



Similarly, comparison of the spectra of thioindoxyl (**17**) and its 5-methyl and 6-chloro derivatives with those of the methyl ethers of

¹⁸⁸ P. Cagniant, M. Mennrath, and D. Cagniant, *Bull. Soc. Chim. France* 989 (1964).

¹⁸⁹ E. Campagne and W. E. Kreighbaum, *J. Org. Chem.* **26**, 359 (1961).

¹⁹⁰ E. Campagne and E. S. Neiss, *J. Heterocyclic Chem.* **2**, 100 (1965).

the corresponding enols, shows that these compounds exist predominantly in the oxo form.¹⁹¹

The spectra of 2,3-dihydrobenzo[*b*]thiophene and its 5-acetyl derivative indicate that the 5-membered ring is strained.¹⁹² The UV spectra of several 4,5,6,7-tetrahydrobenzo[*b*]thiophenes have been given.^{193, 194}

The UV spectra of benzo[*b*]thiophene-4,7-quinone and its 5-hydroxy derivative have been compared with those of their oxygen and selenium analogs.¹⁹⁵

The thermodynamic ionization constants of several hydroxybenzo[*b*]thiophenes have been determined by spectroscopic measurements on the anions.¹⁹⁶

C. PHYSICAL MEASUREMENTS

The physical constants of benzo[*b*]thiophene are given in Table II; the thermal properties were obtained by low temperature calorimetry.

Benzo[*b*]thiophene forms continuous solid solutions with molecules of similar molecular geometry (e.g., indene, indole, or isoquinoline), but eutectics with molecules of significantly different geometry (e.g., 3-methylisoquinoline, 2-methyl- and 2,6-dimethylnaphthalene, or dibenzothiophene).^{197, 198} Naphthalene and benzo[*b*]thiophene form a system of limited solid solutions,^{54, 199} which accounts for the difficulties encountered in their separation (see Section II, B).

¹⁹¹ G. M. Oksengendler and M. A. Mostoslavskii, *Ukr. Khim. Zh.* **26**, 69 (1960); *Chem. Abstr.* **54**, 14934 (1960).

¹⁹² M. J. Y. Foley and N. H. P. Smith, *J. Chem. Soc.* 1899 (1963).

¹⁹³ P. Cagniant and D. Cagniant, *Bull. Soc. Chim. France* 1252 (1955).

¹⁹⁴ P. Cagniant and D. Cagniant, *Bull. Soc. Chim. France* 62 (1953).

¹⁹⁵ C. J. P. Spruit, *Rec. Trav. Chim.* **81**, 810 (1962).

¹⁹⁶ P. Demerseman, R. Reynaud, A. Cheutin, J.-P. Lechartier, C. Pène, A.-M. Laval-Jeantet, R. Royer, and P. Rumpf, *Bull. Soc. Chim. France* 1464 (1965).

^{196a} H. G. Davis and S. Gottlieb, *Fuel* **42**, 37 (1963).

^{196b} H. L. Finke, M. E. Gross, J. F. Messerly, and G. Waddington, *J. Am. Chem. Soc.* **76**, 854 (1954).

¹⁹⁷ V. M. Kravchenko and I. S. Pastukhova, *Dokl. Akad. Nauk, SSSR* **136**, 104 (1961); *Chem. Abstr.* **55**, 15095 (1961).

¹⁹⁸ V. M. Kravchenko, I. S. Pastukhova, and M. I. Mil'skii, *Ukr. Khim. Zh.* **24**, 168 (1958); *Chem. Abstr.* **52**, 15219 (1958).

¹⁹⁹ V. M. Kravchenko and I. S. Pastukhova, *Dokl. Akad. Nauk SSSR* **119**, 285 (1958); *Chem. Abstr.* **52**, 11545 (1958).

Benzo[b]thiophene-1,1-dioxides, but not the 2,3-dihydro-1,1-dioxides or the parent benzo[b]thiophenes, are reduced and can be estimated polarographically.^{200, 201}

TABLE II
PHYSICAL CONSTANTS OF BENZO[b]THIOPHENE

Property	Value ^a	Ref.
Melting point	31.34°	120, 130
Boiling point (760 mm)	219.9°	120, 130
n_D^{20}	1.636	196a
n_D^{35}	1.6332	120, 130, 196b
n_D^{40}	1.6302	120, 130, 196b
d^{20}	1.160 gm/cm ³	196a
d^{35}	1.1988 gm/ml	120, 130, 196b
d^{40}	1.1937 gm/ml	120, 130, 196b
Viscosity		
35°	2.517 centipoises	120, 130
40°	2.423 centipoises	120, 130
Surface tension		
35°	42.6 dynes/cm	120, 130
40°	41.8 dynes/cm	120, 130
Molar volume		
V^{20}	115.7 cm ³ /mole	196a
V^{20}	110.53 ml/mole	120, 130
Molar refractivity		
R_D^{20}	41.48	196a
R_D^{20}	39.93	120, 130
Refractivity intercept	1.0351	120, 130
Parachor (20°)	286.0	120, 130
Entropy		
Liquid at 304.50°K	53.31 cal deg ⁻¹ mole ⁻¹	196b
Solid at 298.16°K	42.33 cal deg ⁻¹ mole ⁻¹	196b
Triple point	304.50°K	196b
Heat of fusion (304.50°K)	2826.8 cal mole ⁻¹	196b
Cryoscopic constant	0.0153 deg ⁻¹	130, 196b

^a All temperatures in degrees Centigrade unless otherwise indicated.

²⁰⁰ H. V. Drushel and J. F. Miller, *Anal. Chem.* **30**, 1271 (1958).

²⁰¹ P. Smith, H. G. Sprague, and O. C. Elmer, *Anal. Chem.* **25**, 793 (1953).

Benzo[*b*]thiophenes may be separated from related compounds by GLC^{23, 202} (see also Section II) and TLC.²⁰³ Benzo[*b*]thiophene-1,1-dioxides are separable by paper chromatography.^{23, 204}

Maxted and Ball²⁰⁵ have studied the adsorption and desorption of benzo[*b*]thiophene on platinum in acetic acid solution. A considerable period is required for the attainment of an adsorption-desorption equilibrium and the required time appears to increase with the concentration of benzo[*b*]thiophene. Thiophene displaces one-third of the benzo[*b*]thiophene from the poisoned catalyst in 24 hours.

Addition of benzo[*b*]thiophenes to solutions used for chemical metallic plating with nickel and cobalt-nickel is said to improve the quality of the metal layer deposited.²⁰⁶

D. STEREOCHEMICAL PROPERTIES OF BENZO[*b*]THIOPHENES

1. *Compounds Possessing Optical Activity*

α -(3-Benzo[*b*]thienyl)propionic acid has been resolved; the levorotatory enantiomer has been shown to have an L-configuration by the fact that it forms a quasiracemate with (+)- α -(1-naphthyl)propionic acid.^{207, 208} α -(2-Benzo[*b*]thienyl)propionic acid also has been resolved; the dextrorotatory enantiomer has been shown to have a D-configuration by relating its configuration to that of (+)- α -methylglutaric acid.²⁰⁹ Examination of the plain rotatory dispersion curves of the dextrorotatory enantiomers of the above compounds supports these assignments of configuration.²¹⁰

X-Ray data have been reported for the racemates of α -(3-benzo[*b*]thienyl)propionic acid and α -(1-naphthyl)propionic acid and for their quasiracemate.²¹¹ The data show that a considerable structural difference exists between the two compounds; consequently their racemates are not isomorphous.

²⁰² J. W. Sweeting and J. K. F. Wilshire, *J. Chromatog.* **6**, 385 (1961).

²⁰³ N. Kucharczyk, J. Fohl, and T. Vymětal, *J. Chromatog.* **11**, 55 (1963).

²⁰⁴ M. Pailer and E. Romberger, *Monatsh. Chem.* **91**, 1070 (1960).

²⁰⁵ E. B. Maxted and G. T. Ball, *J. Chem. Soc.* 2778 (1954).

²⁰⁶ E. Zirngiebl and H. G. Klein, Belgian Patent 613,430 (1962); *Chem. Abstr.* **57**, 14820 (1962).

²⁰⁷ B. Sjöberg, *Arkiv Kemi* **11**, 439 (1957).

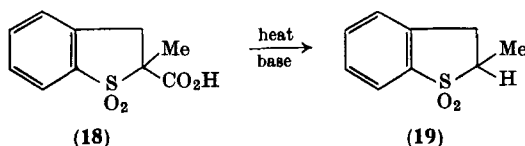
²⁰⁸ B. Sjöberg, *Acta Chem. Scand.* **10**, 1192 (1956).

²⁰⁹ B. Sjöberg, *Arkiv. Kemi* **12**, 565 (1958).

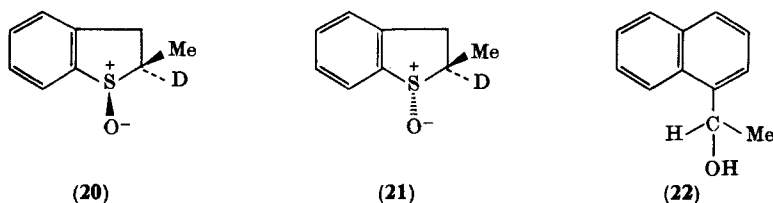
²¹⁰ B. Sjöberg, *Acta Chem.-Scand.* **14**, 273 (1960).

²¹¹ S. Husebye, *Acta Chem. Scand.* **15**, 1215 (1961).

2,3-Dihydrobenzo[b]thiophene-2-carboxylic acid has been resolved²¹²; the levorotatory enantiomer exhibits a plain negative rotatory dispersion curve which allows it to be assigned a D-configuration.²¹³ The corresponding 3-carboxylic acid could not be resolved.²¹²



The sulfone (18) (see Section VI, P) has been resolved.^{214, 215} Unlike open-chain α -sulfonyl carbanions, whose generation and proton capture proceeds with high retention of configuration, Corey *et al.*^{214, 216} found that the carbanion generated by base-catalyzed decarboxylation of (+)-18 gave a "completely racemic sulfone" (19). It was concluded that the lack of stereospecificity of the reaction is evidence for a planar cyclic α -sulfonyl carbanion intermediate. Cram and Whitney^{215, 216} have studied this reaction in some detail; their results indicate that symmetrical (planar) α -sulfonyl carbanions in asymmetric environments are involved as discrete reaction intermediates in the decarboxylation reaction.



Anet *et al.*²¹⁷ have recently used an NMR method to study diastereomeric interaction between either the (+)-sulfoxide (20), or its (−)-isomer (21), and an equimolar amount of the (+)-carbinol (22) (or a

²¹² A. Fredga, *Acta Chem. Scand.* **9**, 719 (1955).

²¹³ B. Sjöberg, *Arkiv Kemi* **15**, 451 (1960).

²¹⁴ E. J. Corey, H. König, and T. H. Lowry, *Tetrahedron Letters* 515 (1962).

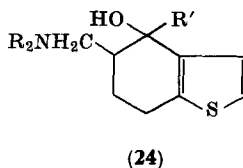
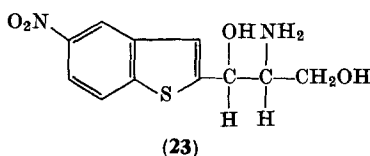
²¹⁵ D. J. Cram and T. A. Whitney, *J. Am. Chem. Soc.* **89**, 4651 (1967).

²¹⁶ D. J. Cram, "Fundamentals of Carbanion Chemistry," p. 109. Academic Press, New York, 1965.

²¹⁷ F. A. L. Anet, L. M. Sweeting, T. A. Whitney, and D. J. Cram, *Tetrahedron Letters* 2617 (1968).

closely related carbinol) in an optically inactive solvent. The hydrogen bonding which is responsible for the diastereomeric interactions is abolished when an excess of dimethyl sulfoxide is added.

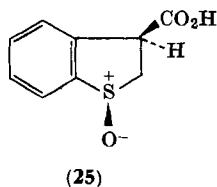
The possibility of optical isomerism arising from restricted rotation (atropisomerism) about the 2,2'-bond in 3-substituted 2-(2-naphthyl)-benzo[*b*]thiophenes has been recognized by Lamberton and McGrail.⁵⁴ Schuetz and Ciporin¹⁶⁴ have interpreted the UV spectra of six 3-aryl-benzo[*b*]thiophenes according to a theory of steric hindrance to free rotation about the pivot bond of the two aromatic rings, but the results are now invalid, since some of the "3-arylbenzo[*b*]thiophenes" used in this study have been shown to be the corresponding 2-isomers (see Section IV, C). No attempt appears to have been made to resolve compounds of this type.



The diastereomers of **23**²¹⁸ and **24**²¹⁹ have been separated by fractional crystallization.

Benzo[*b*]thiophene-2,3-quinone 2-oxime 3-thiosemicarbazone forms asymmetric complexes with nickel and palladium.²²⁰

2. Compounds Exhibiting Geometrical Isomerism



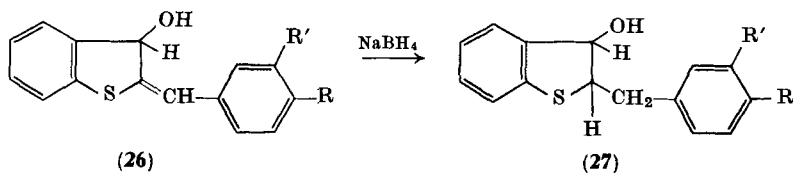
The configurations of *cis*-2,3-dihydrobenzo[*b*]thiophene-3-carboxylic acid 1-oxide (**25**) and its *trans* isomer have been assigned by chemical methods and by use of NMR spectra and ionization constants.²²¹

²¹⁸ S. Rossi and R. Trave, *Farmaco (Pavia), Ed. Sci.* **15**, 396 (1960).

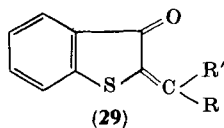
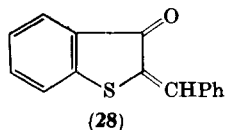
²¹⁹ J. Le Blevec, S. Geiger, and M. Pesson, *Compt. Rend.* **C263**, 817 (1966).

²²⁰ V. Hovorka, Z. Holzbecher, J. Morávek, P. Vlášil, and V. Zátka, *Chem. Listy* **46**, 656 (1952); *Chem. Abstr.* **47**, 8020 (1953).

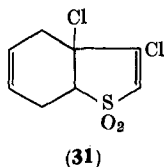
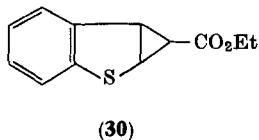
²²¹ E. Jonsson, *Arkiv. Kemi* **26**, 357 (1967).



Reduction of the 2-arylidene-3-hydroxy-2,3-dihydrobenzo[*b*]thiophenes (26; R = R' = Cl, and R = Cl, R' = H) with sodium borohydride affords mixtures of the *cis* and *trans* alcohols (27).²²² The *cis-trans* isomerism exhibited by a number of 2-arylidene-2,3-dihydrobenzo[*b*]thiophen-3-ones (e.g., 28) and by two compounds with the



general formula 29 (R = CO₂Et, R' = CN or COMe) has been studied by Mostoslavskii and co-workers.²²³⁻²²⁷ When a benzene solution of *cis*-2-benzylidene-2,3-dihydrobenzo[*b*]thiophen-3-one (28) is passed through a column packed with a metal oxide or hydroxide, it is converted irreversibly into the *trans* isomer.²²⁴



²²² N. Kucharczyk and V. Horák, *Collection Czech. Chem. Commun.* **33**, 92 (1968).

²²³ V. A. Izmail'skii and M. A. Mostoslavskii, *Ukr. Khim. Zh.* **27**, 234 (1961); *Chem. Abstr.* **55**, 26659 (1961).

²²⁴ M. A. Mostoslavskii, *Ukr. Khim. Zh.* **29**, 1276 (1963); *Chem. Abstr.* **60**, 9127 (1964).

²²⁵ M. A. Mostoslavskii and V. A. Izmail'skii, *Zh. Obshch. Khim.* **31**, 17 (1961); *Chem. Abstr.* **55**, 26659 (1961).

²²⁶ V. A. Izmail'skii and M. A. Mostoslavskii, *Zh. Obshch. Khim.* **31**, 3839 (1961); *Chem. Abstr.* **57**, 9775 (1962).

²²⁷ M. A. Mostoslavskii, V. A. Izmail'skii, and I. N. Shevchuk, *Zh. Obshch. Khim.* **32**, 660 (1962); *Chem. Abstr.* **57**, 14595 (1962).

The *cis* and *trans* isomers of ethyl-2,3-dihydrobenzo[*b*]thiophen-2,3-ylene acetate (**30**)²²⁸ and *cis*- and *trans*-octahydrobenzo[*b*]thiophene²⁷ have been synthesized. Addition of chlorine to the 5,6-double bond of **31** affords a mixture of *cis*- and *trans*-3,3*a*,5,6-tetrachloro-3*a*,4,5,6,7,7*a*-hexahydrobenzo[*b*]thiophene-1,1-dioxide which is separable by fractional crystallization.²²⁹

IV. Preparation of Benzo[*b*]thiophenes by Ring-Closure Reactions

In the following sections we have attempted to classify the methods available for the synthesis of benzo[*b*]thiophenes. (Arylthio)acetaldehyde dialkyl acetals, (arylthio)acetones, aryl phenacyl sulfides, and *S*-arylthioglycolic acids are the most common starting materials. A number of the syntheses, which we have included in Section IV, A, may become general methods in the future, e.g., cyclohexanone and a number of substituted cyclohexanones have been used recently as starting materials.

A. MISCELLANEOUS METHODS

Benzo[*b*]thiophene is formed when thiophenol reacts with acetylene in a heated iron tube²³⁰ or with either ethylene²³¹ or acetylene^{232, 233} in the presence of a heated catalyst. Likewise, with acetylene, methyl phenyl sulfide (thioanisole) affords benzo[*b*]thiophene, while both *p*-thiocresol and di(*p*-tolyl) sulfide afford 5-methylbenzo[*b*]thiophene.²³⁰

Benzo[*b*]thiophene is also formed when hydrogen sulfide is allowed

²²⁸ G. M. Badger, H. J. Rodda, and J. M. Sasse, *J. Chem. Soc.* 4777 (1958).

²²⁹ H. Bluestone, U.S. Patent 3,099,658 (1963); *Chem. Abstr.* **60**, 1704 (1964).

²³⁰ T. Sakan, M. Kotake, A. Fujino, and T. Matsuura, *J. Inst. Polytech., Osaka City Univ.* **C1**, 31 (1950); *Chem. Abstr.* **46**, 2047 (1952); *Nippon Kagaku Zasshi* **73**, 246 (1952); *Chem. Abstr.* **47**, 3293 (1953); T. Me, Japanese Patent 7667 (1951); *Chem. Abstr.* **48**, 731 (1954).

²³¹ T. Lesiak, *Roczniki Chem.* **39**, 757 (1965); *Chem. Abstr.* **63**, 11477 (1965).

²³² T. Lesniak, *Roczniki Chem.* **38**, 1923 (1964); *Chem. Abstr.* **62**, 9090 (1965).

²³³ S. Horie, *Nippon Kagaku Zasshi* **78**, 1171 (1957); *Chem. Abstr.* **54**, 5613 (1960).

to react with styrene,^{199, 234-237} *o*-chlorostyrene,²³⁸ phenylacetylene,²³⁶ ethylbenzene,^{234, 236, 237} *o*-chloroethylbenzene,²³⁸ acetophenone,²³⁶ and α - or β -phenylethylmercaptan²³⁶ in the presence of a suitable heated catalyst. Similar reactions with cumene and *p*-cymene afford 3-methyl- and 3,6-dimethylbenzo[b]thiophene, respectively.^{234, 237} Likewise, 4-chlorobenzo[b]thiophene may be prepared from 2,6-dichlorostyrene, methyl(2,6-dichlorophenyl)carbinol, or 2,6-dichloro- α -methyl- α -toluenethiol.²³⁸ In some cases, mixtures of products are obtained. Thus, benzo[b]thiophene contaminates the products from cumene and *p*-cymene, and 4-chlorobenzo[b]thiophene is found in the products from *o*-chloroethylbenzene and *o*-chlorostyrene. When acetophenone is used, a complex mixture of products arises.

Catalytic dehydrocyclization of 2-ethylthiophenol^{239, 240} and its 4-²³⁹ or 5-amino^{239, 241} derivatives affords benzo[b]thiophene and 5- or 6-aminobenzo[b]thiophene, respectively. 2,3-Dihydrobenzo[b]thiophene is obtained when *o*-ethylphenol reacts with hydrogen sulfide in the presence of a heated catalyst.²⁴²

Reaction of *o*-bromothiophenol with a cuprous acetylide, $\text{CuC}\cdot\text{CR}$ ($\text{R} = \text{Ph}$, *n*-Bu, *n*-Pr, CO_2Et , or CH_2OH), affords a 2-substituted benzo[b]thiophene (2-substituent = R above).²⁴³

When benzyl halides, benzylidene halides, benzotrichloride, or aryl-substituted haloethanes are heated with sulfur, complex mixtures containing thiophenes, benzo[b]thiophenes, and other condensed

²³⁴ J. A. Patterson, R. E. Conary, R. F. McCleary, C. H. Culnane, L. E. Ruidisch, and C. B. Holder, *World Petrol. Congr., Proc.*, 5th, New York, 1959 **4**, 309 (pub. 1960); *Chem. Abstr.* **58**, 4495 (1963); R. F. McCleary and L. W. Devaney, U.S. Patent 2,591,710 (1952); *Chem. Abstr.* **47**, 615 (1953); Texaco Development Corp., British Patent 708,801 (1954); *Chem. Abstr.* **49**, 7003 (1955).

²³⁵ V. M. Kravchenko and V. I. Mil'skii, *Tr. Donetsk. Ind. Inst.* 1959 **39**, 43 (pub. 1960); *Chem. Abstr.* **56**, 1418 (1962).

²³⁶ P. B. Venuto, P. S. Landis, and D. E. Boswell, *Ind. Eng. Chem., Prod. Res. Develop.* **7**, 44 (1968).

²³⁷ L. W. Devaney, U.S. Patent 2,537,446 (1951); *Chem. Abstr.* **45**, 4745 (1951).

²³⁸ H. A. Kaufman and H. M. Foster, U.S. Patent 3,336,335 (1967); *Chem. Abstr.* **68**, 12854 (1968).

²³⁹ C. Hansch, B. Schmidhalter, F. Reiter, and W. Saltonstall, *J. Org. Chem.* **21**, 265 (1956).

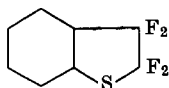
²⁴⁰ G. Frangatos, U.S. Patent 3,271,414 (1966).

²⁴¹ C. Hansch and B. Schmidhalter, *J. Org. Chem.* **20**, 1056 (1955).

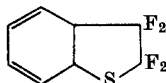
²⁴² P. B. Venuto, U.S. Patent 3,345,383 (1967); *Chem. Abstr.* **68**, 39368 (1968).

²⁴³ A. M. Malte and C. E. Castro, *J. Am. Chem. Soc.* **89**, 6770 (1967).

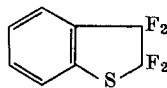
thiophenes may arise.²⁴⁴⁻²⁴⁸ For example, 3-chloro-2-phenylbenzo-[b]thiophene is one of the products of the reaction of either benzylidene chloride or benzotrichloride with sulfur.²⁴⁶



(32)

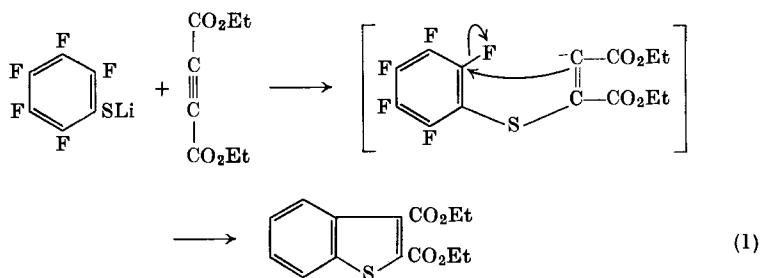


(33)



(34)

Cyclohexene reacts with tetrafluoroethylene and sulfur to give 4,5-tetramethylene-2,2,3,3-tetrafluorothiolane (2,2,3,3-tetrafluoro-octahydrobenzo[b]thiophene) (32).²⁴⁹ Tetrafluoroethylene and sulfur also react with benzene to give mainly perfluorothiolane, together with some 2,2,3,3-tetrafluoro-2,3,3a,7a-tetrahydrobenzo[b]thiophene (33) and the dihydro derivative (34)²⁵⁰; in the presence of iodine more complex products are obtained.²⁵¹



(1)

Diethyl 4,5,6,7-tetrafluorobenzo[b]thiophene-2,3-dicarboxylate is formed when diethyl acetylenedicarboxylate reacts with lithium pentafluorothiophenoxide [Eq. (1)].¹⁰⁹ Similarly, reaction of dimethyl acetylenedicarboxylate with the methyl thiosalicylates (35) affords

²⁴⁴ M. G. Voronkov and V. Udre, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR* 527 (1966); *Chem. Abstr.* **66**, 65344 (1967).

²⁴⁵ M. G. Voronkov and V. Udre, *Khim. Geterotsikl. Soedin., Akad. Nauk. Latv. SSR* 148 (1965); *Chem. Abstr.* **63**, 5581 (1965).

²⁴⁶ E. J. Geering, U.S. Patent 3,278,552 (1966); *Chem. Abstr.* **66**, 10920 (1967).

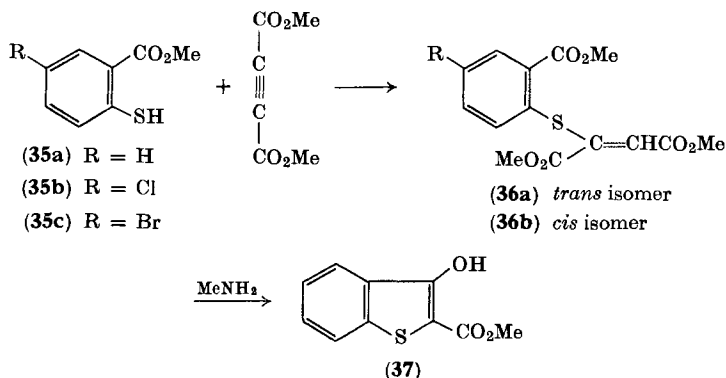
²⁴⁷ M. G. Voronkov and V. Udre, U.S.S.R. Patent 199,909 (1967); *Chem. Abstr.* **68**, 114580 (1968).

²⁴⁸ M. G. Voronkov, V. Udre, and E. Popova, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* 1003 (1967); *Chem. Abstr.* **69**, 96367 (1969).

²⁴⁹ C. G. Krespan, U.S. Patent 3,149,124 (1964); *Chem. Abstr.* **62**, 7728 (1965).

²⁵⁰ C. G. Krespan, U.S. Patent 3,119,836 (1964); *Chem. Abstr.* **60**, 15834 (1964).

²⁵¹ C. G. Krespan, U.S. Patent 2,931,863 (1960).



the *trans* adducts (36a), which are thermally isomerized to the corresponding *cis* adducts (36b).¹⁴⁸ The adducts (36a and 36b) are cyclized by methylamine to the hydroxy esters (37); ammonia will effect these cyclizations only in the case of the *cis* isomers (36b).¹⁴⁸

4,5,6,7-Tetrafluoro-2-methylbenzo[*b*]thiophene has been prepared in 85% yield by heating 2',3',4',5',6'-pentafluorophenylpropane-2,2-dithiol with potassium hydroxide in boiling pyridine (see also Section IV, E).¹⁰⁸

A number of interesting syntheses of benzo[*b*]thiophenes have been reported recently using cyclohexanone and its derivatives as starting materials. Cyclohexanone reacts with nitriles of the type XCH_2CN (where $X = CN, CO_2Et, CONH_2$, or $COPh$) in the presence of sulfur and a secondary amine (e.g., diethylamine or morpholine) to give 3-substituted 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophenes (38) (Scheme 1).^{252, 253} The same products (38) are obtained if 2-mercaptocyclohexanone is condensed with the same nitriles in the presence of a secondary amine,^{252, 253} or if the nitriles are allowed to condense with 2-chlorocyclohexanone in the presence of sodium hydrogen sulfide (Scheme 1).^{254, 255} In a closely related reaction, 2-chloro-1-formylcyclohex-1-ene (39) condenses with ethyl thioglycolate in the presence of triethylamine to give ethyl 4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate (40) (64%).²⁵⁶

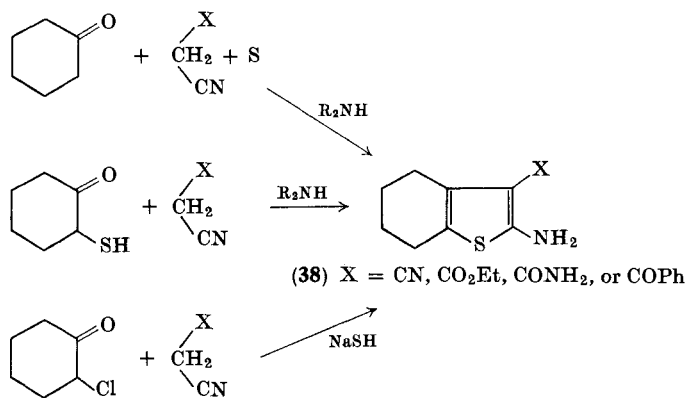
²⁵² K. Gewald, *Z. Chem.* **2**, 305 (1962).

²⁵³ K. Gewald, E. Schinke, and H. Böttcher, *Chem. Ber.* **99**, 94 (1966).

²⁵⁴ K. Gewald, *Z. Chem.* **7**, 186 (1967).

²⁵⁵ K. Gewald, *Chem. Ber.* **98**, 3571 (1965).

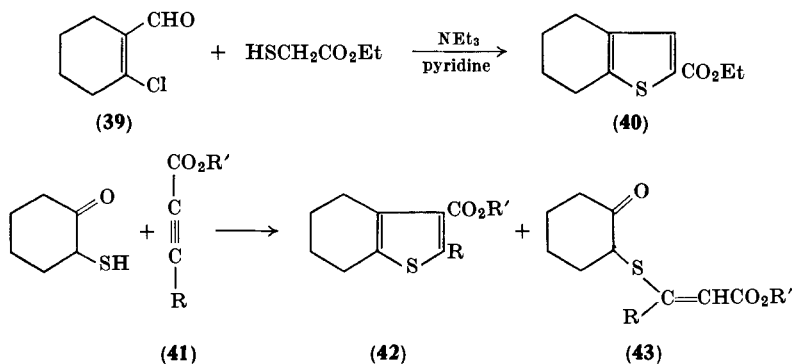
²⁵⁶ S. Hauptmann, M. Weissenfels, M. Scholz, E.-M. Werner, H.-J. Köhler, and J. Weisflog, *Tetrahedron Letters* 1317 (1968).



SCHEME 1

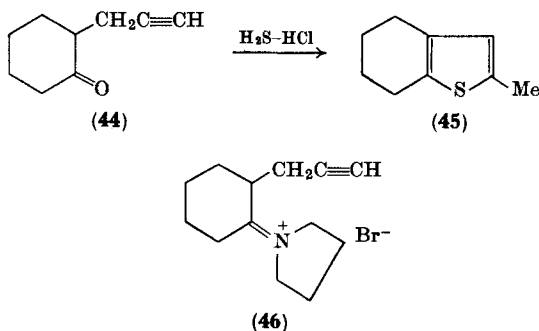
Methyl acetylenecarboxylate (**41**; R = H, R' = Me) reacts with 2-mercaptocyclohexanone in the presence of a catalytic quantity of potassium *tert*-butoxide to give methyl 4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (**42**; R = H, R' = Me), together with a mixture of the *cis* and *trans* isomers of the adduct (**43**; R = H, R' = Me).²⁵⁷ Substituted acetylenecarboxylic acid esters (**41**; R = Me or Ph, R' = Et) behave analogously; only the *cis* adducts (**43**) are formed in these cases.

When 3-mercaptocyclohexanone condenses with dichloroacetaldehyde or chloroacetaldehyde in the presence of a catalytic quantity of acid (e.g., *p*-toluenesulfonic acid), simultaneous cyclization occurs to give 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one (see Section VI, B, 4) and 2,4,5,6,7,7 α -hexahydrobenzo[*b*]thiophen-4-one (see Section

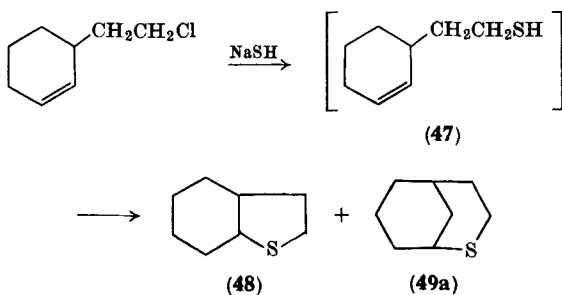


²⁵⁷ F. Bohlmann and E. Bresinsky, *Chem. Ber.* **97**, 2109 (1964).

VI, B, 5), respectively.²⁵⁸ The latter product is also obtained by acidic hydrolysis of the condensation product of 3-mercaptocyclohexanone ethylene ketal and chloroacetaldehyde.²⁵⁹



A mixture of hydrogen sulfide and hydrogen chloride effects cyclization of 2-propynylcyclohexanone (44) to 2-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene (45) (69%).²⁶⁰ Treatment of 46 with either hydrogen sulfide or carbon disulfide also affords 45, but in lower yields. A 5% yield of 45 is obtained, together with 10% 2-methyl-4,5,6,7-tetrahydrobenzofuran, when phosphorus pentasulfide is used to effect cyclization of 44.



A mixture of *cis*-octahydrobenzo[b]thiophene (48) and *cis*-2-thiabicyclo[3.3.2]nonane (49a) results from the treatment of 3-β-chlo-

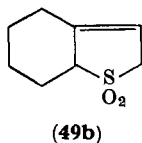
²⁵⁸ H. M. Foster, R. P. Napier, and C.-C. Chu, U.S. Patent 3,346,591 (1967); *Chem. Abstr.* **68**, 78126 (1968).

²⁵⁹ H. M. Foster and R. P. Napier, U.S. Patent 3,357,997 (1967); *Chem. Abstr.* **69**, 2863 (1968).

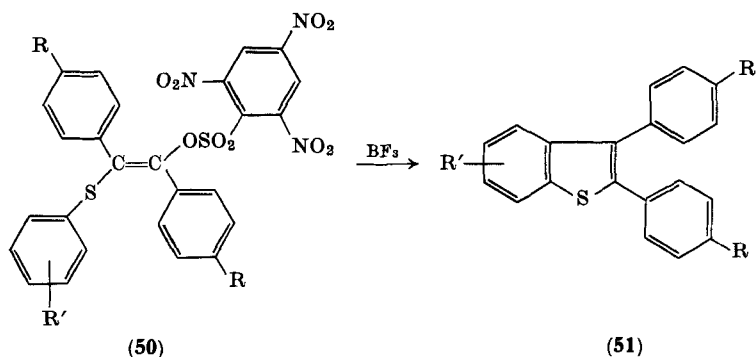
²⁶⁰ K. E. Schulte, J. Reisch, and D. Bergenthal, *Chem. Ber.* **101**, 1540 (1968).

roethyleyclohex-1-ene with sodium hydrogen sulfide.²⁶¹ Compound **47** is probably an intermediate in this reaction since it can be prepared unambiguously, and also gives the same products on cyclization.

The sulfone (**49b**) is obtained on treatment of 1-vinylcyclohexene with sulfur dioxide.²⁷



Until quite recently, few 2,3-diarylbenzo[*b*]thiophenes had been prepared. 2,3-Di(*p*-methoxyphenyl)benzo[*b*]thiophene is obtained in only 1.9% yield by heating a mixture of anisoin, thiophenol, and



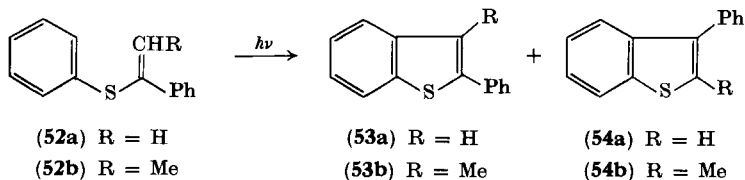
polyphosphoric acid (PPA).²⁶² However, the adducts (**50**) of aryl-sulfenyl 2,4,6-trinitrobenzenesulfonates ($R' = \text{H}$, *p*-Me, *p*-OMe, *p*-Cl, or *m*-Cl) and tolane or 4,4'-dimethyltolane ($R = \text{H}$ or Me) are said to cyclize in the presence of boron trifluoride to give the corresponding 2,3-diarylbenzo[*b*]thiophenes (**51**) in almost theoretical yield.²⁶³ When R' is *para* to the vinylmercapto group, cyclization affords

²⁶¹ N. P. Volynskii, G. D. Gal'pern, and A. B. Urin, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* 1031 (1967); *Chem. Abstr.* **69**, 77035 (1968).

²⁶² J. Szmuszkowicz, E. M. Glenn, R. V. Heinzelman, J. B. Hester, and G. A. Youngdale, *J. Med. Chem.* **9**, 527 (1966).

²⁶³ G. Capozzi, G. Melloni, G. Modena, and M. Piscitelli, *Tetrahedron Letters* 4039 (1968).

6-substituted benzo[*b*]thiophenes by rearrangement, and not the expected 5-substituted compounds. When $R = H$ and $R' = m\text{-Cl}$, a mixture of 4- and 6-chloro-2,3-diphenylbenzo[*b*]thiophene is obtained.



Photoirradiation of the (phenylthio)ethylenes (52a or 52b) in each case affords a low yield of a mixture of the "normal" product (53a or 53b, respectively) and the "abnormal" product (54a or 54b, respectively) together with products of higher molecular weight.⁹⁷ No "abnormal" products are obtained when the 2-phenyl group of 52 is replaced by H or Me. Mechanisms have been proposed to account for these observations.

Bis(dithiobenzil)nickel decomposes on being heated at 292° to give (exclusively) 2-phenylbenzo[*b*]thiophene (95%).^{263a, 263b} Related metal complexes (e.g., those of Pd and Pt) behave similarly. In some cases (e.g., Pd) a mixture of 2-phenylbenzo[*b*]thiophene and tetraphenylthiophene is obtained.

Bergmann and Meyer²⁶⁴ cyclized the 1,1-diarylpropenes (55; $R = H$ or Cl) to the corresponding benzo[*b*]thiophene-1,1-dioxides (56; $R = H$ or Cl) using sulfuric acid. 3-Phenylbenzo[*b*]thiophene-1,1-dioxide is obtained by cyclization of the *trans* isomer of 57 under Friedel-Crafts conditions.^{265, 266} Similar cyclization of 58 ($R = H$ ²⁶⁷ or $\text{CH}_2\text{CH}_2\text{Ph}$ ²⁶⁸) affords the corresponding 2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide. Thioindoxyl-1,1-dioxide (60) is obtained in 81%

^{263a} G. N. Schrauzer and V. P. Mayweg, *J. Am. Chem. Soc.* **87**, 1483 (1965) and references cited therein.

^{263b} V. P. Mayweg, Ph.D. Thesis, University of Munich (1964).

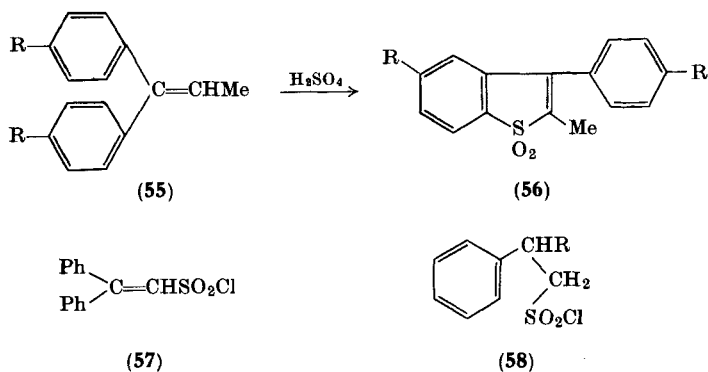
²⁶⁴ E. D. Bergmann and A. M. Meyer, *J. Org. Chem.* **30**, 2840 (1965).

²⁶⁵ F. G. Bordwell and M. L. Peterson, *J. Am. Chem. Soc.* **81**, 2000 (1959).

²⁶⁶ A. P. Terent'ev and R. A. Gracheva, *Zh. Obshch. Khim.* **31**, 217 (1961); *Chem. Abstr.* **55**, 22205 (1961).

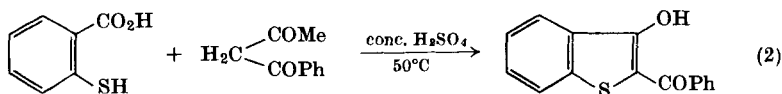
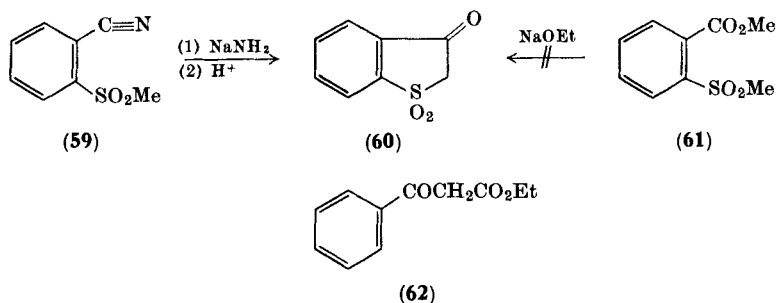
²⁶⁷ W. E. Truce and J. P. Milonis, *J. Am. Chem. Soc.* **74**, 974 (1952).

²⁶⁸ W. E. Truce, D. D. Emrick, and R. E. Miller, *J. Am. Chem. Soc.* **75**, 3359 (1953).



yield by Thorpe cyclization of *o*-methylsulfonylbenzonitrile (**59**)²⁶⁹; it cannot be obtained by Claisen cyclization of the ester (**61**).²⁷⁰ Treatment of the ester (**62**) with oleum gives 2-(ethoxycarbonyl)thioindoxyl-1,1-dioxide (82%).²⁷¹

Thiosalicylic acid condenses with benzoylacetone in the presence of concentrated sulfuric acid to give 2-(benzoyl)thioindoxyl [Eq. (2)].²⁷²

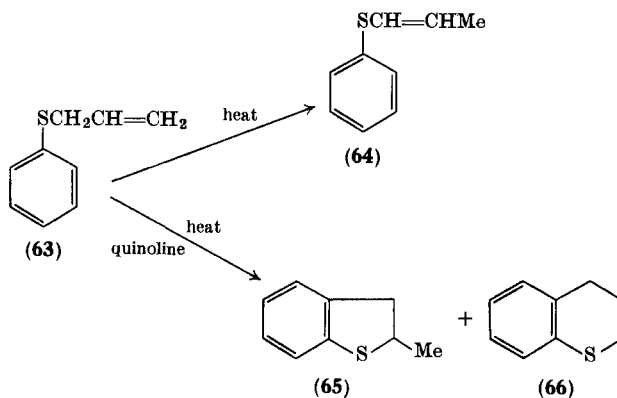


²⁶⁹ W. E. Truce, W. W. Bannister, and R. H. Knospe, *J. Org. Chem.* **27**, 2821 (1962).

²⁷⁰ W. E. Truce and R. H. Knospe, *J. Am. Chem. Soc.* **77**, 5063 (1955).

²⁷¹ M. A. Matskanova and G. Ya. Vanags, *Dokl. Akad. Nauk SSSR* **132**, 615 (1960); *Chem. Abstr.* **54**, 24636 (1960).

²⁷² Aktiebolaget Hassle, Apotekare Paul Nordstroms Fabriker, British Patent 1,101,946 (1968).



Claims that 2-methyl-2,3-dihydrobenzo[b]thiophene (65) and 2-methyl-2,3-dihydrobenzo[b]thiophene-1,1-dioxide, respectively, are the products of heating allylphenyl sulfide (63)²⁷³ and its sulfone²⁷⁴ have not been substantiated. In the former case the product is 64^{275, 276}; in the latter case the corresponding sulfone is obtained.²⁷⁷ However, 65 (25%), together with thiachroman (66) (30%), may be obtained by heating 63 in either *N,N*-diethylaniline or quinoline.^{275, 278–280} Likewise, allyl *p*-tolyl sulfide and allyl *o*-tolyl sulfide afford mixtures of 2,5-dimethyl-2,3-dihydrobenzo[b]thiophene and 6-methylthiachroman, and 2,7-dimethyl-2,3-dihydrobenzo[b]thiophene and 8-methylthiachroman, respectively.²⁸⁰ These reactions probably involve a thio-Claisen rearrangement of the starting materials to *o*-allylthiophenols, which spontaneously cyclize under the reaction conditions. The only thio-Claisen rearrangement accomplished to date

²⁷³ H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 35. Wiley (Interscience), New York, 1954.

²⁷⁴ H. J. Backer and N. Dost, *Rec. Trav. Chim.* **68**, 1143 (1949).

²⁷⁵ H. Kwart and C. M. Hackett, *J. Am. Chem. Soc.* **84**, 1754 (1962).

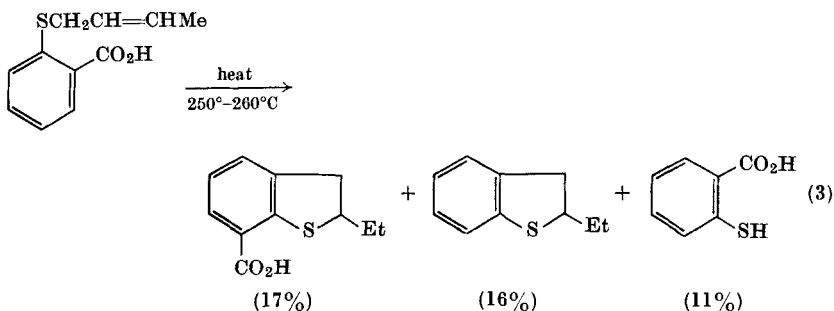
²⁷⁶ E. N. Karaulova, D. Sh. Meilanova, and G. D. Gal'pern, *Dokl. Akad. Nauk SSSR* **113**, 1280 (1957); *Chem. Abstr.* **52**, 301 (1958); *Zh. Obshch. Khim.* **27**, 3034 (1957); *Chem. Abstr.* **52**, 8074 (1958).

²⁷⁷ E. N. Karaulova, D. Sh. Meilanova, and G. D. Gal'pern, *Zh. Obshch. Khim.* **29**, 662 (1959); *Chem. Abstr.* **54**, 445 (1960).

²⁷⁸ C. Y. Meyers, C. Rinaldi, and L. Bonoli, *J. Org. Chem.* **28**, 2440 (1963).

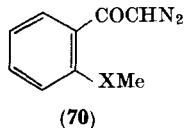
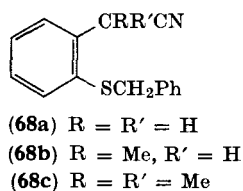
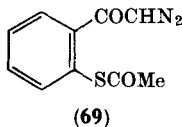
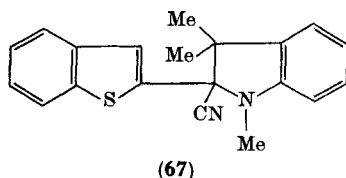
²⁷⁹ C. Y. Meyers, *8th Ann. Rept. Res., Petrol. Res. Fund. Am. Chem. Soc.* **58** (1963).

²⁸⁰ E. N. Karaulova, G. D. Gal'pern, V. D. Nikitina, and I. V. Cherepanova, *Neftekhimiya* **7**, 774 (1967); *Chem. Abstr.* **68**, 78056 (1968).



without an amine solvent has been the thermal rearrangement of *S*-crotylthiosalicylic acid [Eq. (3)]²⁸¹; a mixture of *o*-mercaptobenzoic acid, 2-ethyl-2,3-dihydrobenzo[*b*]thiophene-7-carboxylic acid, 2-ethyl-2,3-dihydrobenzo[*b*]thiophene, and 2-methylthiachroman is obtained.^{281, 282} An amine solvent inhibits product formation in this case, and esterification of the carboxyl group completely suppresses the rearrangement.²⁸² Recently, Kwart and Cohen²⁸² have suggested that the *ortho* carboxyl group influences the rearrangement; several allylphenyl sulfides undergo thio-Claisen rearrangements in octanoic acid. The reaction products using quinoline or octanoic acid are identical; the reactions differ only in rate and product proportions.

Attempts to prepare benzo[*b*]thiophenes by a route analogous to the Fischer indole synthesis have been unsuccessful.²⁸³



²⁸¹ J. C. Petropoulos, M. A. McCall, and D. S. Tarbell, *J. Am. Chem. Soc.* **75**, 1130 (1953).

²⁸² H. Kwart and M. H. Cohen, *Chem. Commun.* 319 (1968).

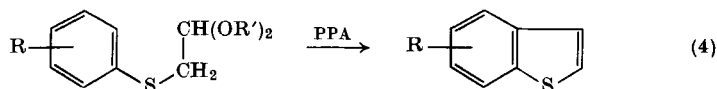
²⁸³ D. Kaminsky, J. Shavel, and R. I. Meltzer, *Tetrahedron Letters* 859 (1967).

o-Thiocyanatobenzaldehyde undergoes condensation with 1,3,3-trimethyl-2-methyleneindoline to give the nitrile (67), which has been synthesized unambiguously from 2-benzo[*b*]thienyllithium and 1,3,3-trimethyloxindole.²⁸⁴

Thioether cleavage of 68a with aluminum bromide in benzene¹¹² or ethereal hydrogen chloride²⁸⁵ affords 2-aminobenzo[*b*]thiophene in high yield. Similar cleavage of 68b and 68c gives 2-amino-3-methylbenzo[*b*]thiophene and the imine (14), respectively.¹¹³

The diazoketone (69) affords thioindoxyl (17) on treatment with hydrochloric acid²⁸⁶; unlike its oxygen analog, which can be obtained by cyclization of 70 (X = O) with acid, thioindoxyl cannot be obtained by cyclization of the related compound (70) (X = S).²⁸⁶

B. CYCLIZATION OF (ARYLTHIO)ACETALDEHYDE DIALKYL ACETALS



The synthesis of benzo[*b*]thiophenes by the PPA-promoted cyclization of (arylthio)acetaldehyde dimethyl or diethyl acetals [Eq. (4)] was introduced by Tilak^{287, 288} in 1950 and improved in 1951.²⁸⁹ The acetals are readily prepared from aryl mercaptans and bromoacetaldehyde dimethyl (or diethyl) acetal in the presence of sodium ethoxide, or by reaction of an aryllithium compound with [(MeO)₂CHCH₂S]₂.²⁹⁰ Diethyl acetal as starting material sometimes gives better yields of product than the corresponding dimethyl acetal.²⁹¹ Optimum yields of benzo[*b*]thiophenes are obtained when cyclization of the acetals is carried out under reduced pressure so that the lower boiling benzo[*b*]thiophenes distill as soon as they are formed. Experimental conditions for obtaining optimum yields vary from case

²⁸⁴ R. C. Bertelson, *J. Org. Chem.* **30**, 2875 (1965).

²⁸⁵ G. W. Stacy and D. L. Eck, *Tetrahedron Letters* 5201 (1967).

²⁸⁶ J. N. Chatterjea and K. Prasad, *J. Indian Chem. Soc.* **31**, 203 (1954).

²⁸⁷ B. D. Tilak, *Proc. Indian Acad. Sci.* **32A**, 390 (1950).

²⁸⁸ A similar approach was begun by Banfield *et al.*²⁹¹ in 1948 but the results of this work were not reported until 1956.

²⁸⁹ K. Rabindran and B. D. Tilak, *Current Sci. (India)* **20**, 205 (1951); K. Rabindran and A. V. Sunthakar, *Bombay Technologist* **2**, 84 (1952).

²⁹⁰ L. J. Pandya and B. D. Tilak, *Chem. Ind. (London)* 981 (1958); *J. Sci. Ind. Res. (India)* **18B**, 371 (1959).

²⁹¹ J. E. Banfield, W. Davies, B. C. Ennis, S. Middleton, and Q. N. Porter, *J. Chem. Soc.* 2603 (1956).

TABLE III
 BENZO[*b*]THIOPHENES BY RING-CLOSURE OF
 (ARYLTHTIO)ACETALDEHYDE DIALKYL ACETALS [Eq. (4)]

Substituents	Melting point and/or boiling point (°C)	Yield (%)	Ref.
None	30–32	37, 72.5	287, 289
2-Me	51–52	80.5	204
5-Me	37–38 (125–135/3 mm)	48.5, 61, ?	295, 292, 95
6-Me ^a	114–115° (110–115/4 mm)	78, 42, 77	287, 295, 292
4-Me) _b	(120/18 mm)	?	95 ^d
6-Me)	42–43		
7-Me	(112/16 mm)	53, 79, ?	295, 90, 95
2-Et	(118–125/10 mm)	95	204
5-Et	88–89° (86–88/2 mm)	66	292
5-Pr ^t	110–112° (89–91/0.5 mm)	69	292
5-Bu ^t	116–118° (102/0.6 mm)	59	292
2,5-Me ₂	52–52.5	93	204
2,6-Me ₂	61.5–62 (98–102/9 mm)	86	204
2,7-Me ₂	(132–136/11 mm)	79	204
4,7-Me ₂	(106–112/8 mm)	72	204
5,7-Me ₂	(117–120/10 mm)	52	204
6,7-Me ₂	(116–120/9 mm)	72	204
2,4,7-Me ₃	(122–125/9 mm)	83	204
2,5,7-Me ₃	(130–137/9 mm)	79	204
2,6,7-Me ₃	32–32.5 (118–122/9 mm)	92	204
5-Ph	100 (170–210/1.5 mm)	79	305
4-Cl	(125/15 mm)	32	295, 241
5-Cl	34–36 (85/4 mm)	43, 70	295, 144
7-Cl	(115/10 mm)	40	295

to case (see, e.g., El Shanta and Scrowston¹⁴⁴ and Chapman *et al.*²⁹²). The method is of wide application (Table III); its uses for preparing benzo[*b*]thiophenes and other condensed thiophene systems have been reviewed by Tilak.²⁹³ Cyclizations of *ortho*- and *para*-substituted (arylthio)acetaldehyde dialkyl acetals unambiguously give 7- and 5-substituted benzo[*b*]thiophenes, respectively; *meta*-substituted starting materials invariably afford mixtures of 4- and 6-substituted

²⁹² N. B. Chapman, K. Clarke, B. Gore, and S. N. Sawhney, *J. Chem. Soc., C* 514 (1968).

²⁹³ B. D. Tilak, *Tetrahedron* **9**, 76 (1960).

TABLE III—*continued*

Substituents	Melting point and/or boiling point (°C)	Yield (%)	Ref.
5-Br	47–47.5	13,49,60,38	488, 291, 144, 76
7-Br	(108–109/10 mm)	72, 39	289, 488
	(137–138/10 mm)	36	105
4-Br	31–32 (115.5–117/5 mm)	75, 58	294, 105
6-Br	57		
2-Me, 5-Br	91–92	38	76
5-Me, 7-Br	(128–129/5 mm)	71	106
7-Me, 5-Br	(100–101/3 mm)	72	106
4-Me, 5-Br	45–46	65	106
6-Me, 5-Br	93–94		
5-Me, 6-Br	91–92	66	106
5-Me, 4-Br	52–53		
5-OMe	42–43 (85–90/0.5 mm)	Low	617
6-OMe	(145–155/15 mm)	62, 85	617, 618
7-OMe	(140–145/15 mm)	18	617
5-OEt	(145/12 mm)	15	617
5-Me, 6-OMe	62–63 (160/12 mm)	64	617
5,6-(OMe) ₂	100–101	23	291
5-NO ₂	149	12	488
5-Me, 2-S-(C ₆ H ₄ Me- <i>p</i>)	Oil	23	300

^a Probably a mixture with the 4-methyl isomer.

^b A 1:2 mixture of the 4- and 6-isomer, respectively.

^c Melting point of picrate.

^d See also Sunthakar and Tilak.²⁹⁵

benzo[b]thiophenes,^{95, 106, 241, 294} and not exclusively the 6-isomers as originally suggested.^{287, 295}

The PPA-promoted cyclizations of (phenylthio)acetaldehyde dimethyl acetal and α -(phenylthio)propionaldehyde diethyl acetal yield benzo[b]thiophene together with 3-methoxy-2,3-dihydrobenzo[b]thiophene, and a mixture of 2- and 3-methylbenzo[b]thiophene, respectively.²⁹⁶ Mechanisms have been proposed to account for these results.

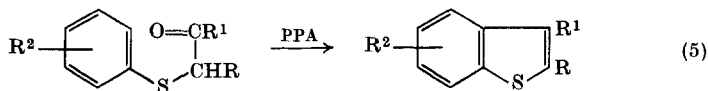
Stannic chloride has been used successfully to cyclize a few (arylthio)acetaldehyde diethyl acetals.²⁹¹

²⁹⁴ R. L. Titus, M. Choi, and P. M. Hutt, *J. Heterocyclic Chem.* **4**, 651 (1967).

²⁹⁵ A. V. Sunthakar and B. D. Tilak, *Proc. Indian Acad. Sci.* **32A**, 396 (1950).

²⁹⁶ D. S. Rao, *4th Ann. Rept. Res., Petrol. Res. Fund., Am. Chem. Soc.* 90 (1959).

C. CYCLIZATION OF (ARYLTHIO)ACETONES AND
ARYL PHENACYL SULFIDES



In 1949, Werner¹⁸⁷ announced the synthesis of several 3-alkyl- and 2,3-dialkylbenzo[*b*]thiophenes by the cyclodehydration of (arylthio)-acetones with phosphorus pentoxide or zinc chloride [Eq. (5)]. The reaction has since been widely used to synthesize alkyl- and aryl-substituted benzo[*b*]thiophenes (Table IV). Cyclodehydration proceeds most conveniently with PPA,^{297, 298} but concentrated sulfuric acid,^{299, 300} hydrofluoric acid,²⁹⁹ aluminum chloride in benzene³⁰¹ or chlorobenzene,³⁰² zinc chloride and hydrochloric acid,³⁰³ a melt of aluminum and sodium chlorides,³⁰⁴ and phosphorus pentoxide in boiling *o*-dichlorobenzene³⁰⁵ have been less widely used.

Cyclodehydrations of *ortho*- or *para*-substituted (arylthio)acetones afford 7- and 5-substituted 3-methylbenzo[*b*]thiophenes, respectively; *meta*-substituted (arylthio)acetones afford mixtures of 4- and 6-substituted 3-methylbenzo[*b*]thiophenes (see, e.g., Matsuki and Ito¹⁰⁵). However, in these cases a partial migration of the 3-methyl group to the 2-position may be an added complication.^{297, 306} Such isomerizations occur during the preparation of 3-methylbenzo[*b*]thiophene and its 5-alkyl,^{297, 306} but not its 5-halo²⁹⁷ derivatives. A mixture of 3-methylbenzo[*b*]thiophene and its 5- (the expected product) and 6-*tert*-butyl derivatives is obtained on cyclization of (*p*-*tert*-butyl-

²⁹⁷ R. P. Dickinson and B. Iddon, *J. Chem. Soc., C* 2733 (1968).

²⁹⁸ N. B. Chapman, K. Clarke, and S. N. Sawhney, *J. Chem. Soc., C* 518 (1968).

²⁹⁹ O. Dann and M. Kokorudz, *Chem. Ber.* **91**, 172 (1958).

³⁰⁰ V. Prey, Austrian Patent 195,421 (1958); *Chem. Abstr.* **52**, 9216 (1958).

³⁰¹ Ya. L. Gold'farb and V. P. Litvinov, *Byul. Izobret. i Tovarnykh Znakov* **14** (1963); U.S.S.R. Patent 157,981 (1963); *Chem. Abstr.* **60**, 10651 (1964).

³⁰² Gevaert-Agfa N.V., Netherlands Patent Appl. 6,701,552 (1967); *Chem. Abstr.* **68**, 87865 (1968).

³⁰³ F. Quint and G. Schäfer, German Patent 864,559 (1953); *Chem. Abstr.* **52**, 16369 (1958).

³⁰⁴ G. Schäfer and F. Quint, German Patent 871,452 (1953).

³⁰⁵ L. J. Pandya, D. S. Rao, and B. D. Tilak, *J. Sci. Ind. Res. (India)* **18B**, 516 (1959).

³⁰⁶ D. S. Rao and B. D. Tilak, *Ann. Rept., Am. Petrol. Inst. Res. Project* **48**, No. 7, 54 (1954); reference taken from Rao and Tilak.¹⁸⁶

TABLE IV. BENZO[b]THIOPHENES BY RING-CLOSURE OF (ARYLTHIO)ACETONES OR ARYL PHENACYL SULFIDES [Eq. (5)]

Substituents	Melting point and/or boiling point (°C)	Yield (%)	Ref.
3-Me	(112/12 mm)	70-90	277, 299, 301, 314a, 489, 521, 664, 741
3-Et	(143/24 mm)	90-95, 82, 87	314a, 742, 664
3-Pr ⁱ	(69-70/0.1 mm)	84	358
2,3-Me ₂	(96-98/1.5 mm)	82	100, 664
3,5-Me ₂	(127/14 mm)	69, 84, 68, 27, 90-95, ?	489, 664, 299, 307, 314a, 745
3,6-Me ₂	(133-134/18 mm)	63	307
3,7-Me ₂	30-31, (122-124/12 mm)	60	307
5-Me, 3-Et	?	90-95	314a
7-Me, 3-Et	(137-138/13 mm)	94.5	664
3-Me, 5-Bu ^t } _a	(145-175/12 mm)	?	104
3-Me, 6-Bu ^t }	?	?	
3,5-Et ₂	(163-164/12 mm)	83	314a
2,3,5-Me ₃	57.5, (145-146/15 mm)	93	664
2,3,6-Me ₃	(126-135/9 mm)	75	204
2,3,7-Me ₃	53.5, (143-144/15 mm)	91	664
3,4,7-Me ₃	53-53.5, (150/10 mm)	80-90, 81	139, 204
3,5,7-Me ₃	(150/20 mm)	80-90, 92	139, 204
3,6,7-Me ₃	47-48, (125-129/9 mm)	71	204
2,3,4-Me ₃ } _a	?	?	136
2,3,6-Me ₃ }	?		
2,3-Me ₂ , 5-Et	(160-161/16 mm)	87	314b
5,7-Me ₂ , 3-Et	(147-148/8 mm)	88	314b
2,3-Me ₂ , 5-Bu ^t }	39.5	?	
2,3-Me ₂ , 6-Bu ^t }	?	20-30	104
2,3,4,7-Me ₄	65-67.5, (150-155/9 mm)	70.5, 80-90	204, 139
2,3,5,7-Me ₄	59.5, (156/15 mm)	96, 76.5	664, 204
2,3,6,7-Me ₄	107-109, (141-148/10 mm)	81.5	204
2,3,4,7-Me ₄ , 5-Et	72, (186/16 mm)	80-90	139

continued

TABLE IV—continued

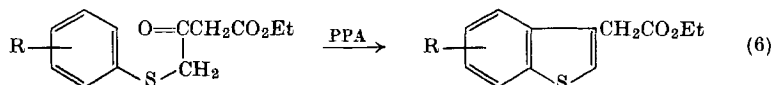
Substituents	Melting point and/or boiling point (°C)	Yield (%)	Ref.
2,3,4,7-Me ₄ , 6-Et	51, (131/20 mm)	80–90	139
2,3,5,7-Me ₄ , 4-Et	67.5–68, (188/17 mm)	60	139
2-Ph	175–176	32, 24, ?, 90	307, 299, 303, 304
3-Ph	(148–152/1.75 mm)	65, 60	299, 186
2-Ph}	175–176	47	186
3-Ph}	(130–132/0.5 mm)	26	
2-(2-Naphthyl)}	212	13	
3-(2-Naphthyl)}	59	38	308, 309
2-(2-Naphthyl)}	212	4	
3-(1-Naphthyl)}	92	36	308, 309
2-(2-Thienyl)}	156	16	
3-(2-Thienyl)}	(160–165/2.5 mm)	32	308, 309
2-(3-Benzo[b]thienyl)	76	?	305, 308
3-(3-Benzo[b]thienyl)	84	?	305
2-(C ₆ H ₄ Br- <i>p</i>)	205	?	302
2-(C ₆ H ₄ OMe- <i>p</i>)	193–194	44	307
2-(C ₆ H ₄ OMe- <i>p</i>)}	193	34	
3-(C ₆ H ₄ OMe- <i>p</i>)}	(130–135/0.1 mm)	13	309
3-Me, 2-Ph	77–78	?	447
5-Me, 2-Ph	158–159	37, 26	299, 307
6-Me, 2-Ph	184–184.5	28	307
2-Me, 3-Ph	(145–150/3 mm)	82	309
5-Me, 3-Ph	(110–130/0.3 mm)	77	299
5-Me, 2-Ph}	156–157	36	
5-Me, 3-Ph}	(134–137/0.5 mm)	25	186
5,7-Me ₂ , 3-Ph	161–162, (175–177/1.2 mm)	88	314b
3-Me, 5-Br	40–41, (151–152/10 mm)	31, 31, 47, ?, 70	105, 76, 489, 570, 298
3-Me, 4-Br}	92–93	11	
3-Me, 6-Br}	(138–139/4 mm)	31	105
3-Me, 7-Br	(129–130/5 mm)	38, 80	105, 298

3-Me, 5-Cl	32-34, (92-93/0.3 mm)	55, ?, 65	489, 570, 298
3-Me, 7-Cl	(110/2 mm)	82	298
3-Me, 5-F	(94/4 mm)	64	298
3-Me, 4,5,6,7-F ₄	62-63	74	491
2,3-Me ₂ , 5-Br	100.5, (179/12 mm)	82, 60-70	81, 492
2,3-Me ₂ , 6-Br	(174.5/13.5 mm)	77	81
2,3-Me ₂ , 5-Cl	80, (157/12 mm)	85, 60-70	81, 492
2,3,4,7-Me ₄ , 5-Br	97, (177/1 mm)	65	81
2-Ph, 5-Br	186-187	35	76
4-Me, 2-Ph, 5,7-Cl ₂	114.5-115	?	303
3-Me, 5-OMe	(149/11 mm)	18	314c
3-Me, 6-OMe	(162/20 mm)	76	314c
3-Me, 7-OMe	77, (142/7 mm)	45	314c
2,3-Me ₂ , 5-OMe	(162/13 mm)	36	314c
2,3-Me ₂ , 6-OMe	69, (170/16 mm)	33.5	314c
2,3-Me ₂ , 7-OMe	108, (159/12 mm)	75.5, ?	314c, 615
3,7-Me ₂ , 5-OMe	52.5, (170/18 mm)	47.5	615
2,3-Me ₂ , 4-Et, 7-OMe	61, (196-197/20 mm)	?	615
3-Me, 5,6-(OMe) ₂	107-107.5	83	307
2-Ph, 6-OH	?	?	307
2-Ph, 6-OMe	58-59	?	307
2-Ph, 5,6-(OMe) ₂	116.5-117	27	307
2-(C ₆ H ₄ OMe- <i>p</i>), 5,6-(OMe) ₂	85-86	53	307
5-Me, 3-S(C ₆ H ₄ Me- <i>p</i>)	37-38	?	702, 703
3-CH ₂ CO ₂ Et	(130-145/0.4 mm)	?	299
3-CH ₂ CO ₂ Et, 5-Br	56-58, (130-140/10 ⁻³ mm)	?	311
3-CH ₂ CO ₂ Et, 5-Cl	61-62, (140-145/10 ⁻³ mm)	?	311
3-CH ₂ CO ₂ Et, 5-Me	(120-130/10 ⁻³ mm)	?	351
3-CH ₂ CO ₂ Et, 6-OMe	(125-130/10 ⁻³ mm)	?	313
3-CH ₂ CO ₂ Et, 5,6-(OMe) ₂	75-76 (165-170/10 ⁻³ mm)	?	310
3-CH ₂ CO ₂ Et, 4,5,6-(OMe) ₃	Oil (160-170/10 ⁻³ mm)	?	310
3-CH ₂ CO ₂ Et, 4-OMe	?	90.5	143, 312
3-CH ₂ CO ₂ Et, 6-OMe	?		

^a Obtained as a 4:6 mixture.

phenylthio)acetone with phosphorus pentoxide¹⁰⁴; 3-(*p*-*tert*-butyl-phenylthio)butan-2-one affords a similar mixture of products.

Attempted preparation of 3-phenylbenzo[*b*]thiophenes by an extension of the above method invariably proceeds with rearrangement to give the 2-phenyl isomer^{186, 299, 303, 304, 307, 308} or a mixture of the 2- and 3-phenyl isomers.^{186, 308} In this case, use of PPA appears to favor formation of the 3-isomer,^{186, 299, 309} whereas use of hydrofluoric acid usually affords the 2-isomer.²⁹⁹ It is interesting to note that 3-phenylbenzo[*b*]thiophene is converted into its 2-isomer by hydrofluoric acid,²⁹⁹ but is only isomerized to a small extent by hot PPA.^{186, 308} During the cyclization of phenyl phenacyl sulfide to give 2- and/or 3-phenylbenzo[*b*]thiophene, small amounts of diphenyl disulfide and 5-phenylmercapto-3-phenylbenzo[*b*]thiophene are also formed.^{186, 299} 3,3'-Dibenzo[*b*]thienyl,³⁰⁵ 2,3'-dibenzo[*b*]thienyl,³⁰⁵ and mixtures of 2- and 3-(2-thienyl)benzo[*b*]thiophene, 2- and 3-(2-naphthyl)benzo[*b*]thiophene, and 3-(1-naphthyl)- and 2-(2-naphthyl)benzo[*b*]thiophene³⁰⁹ have been prepared by the appropriate modification of the Werner procedure.



Ethyl 3-benzo[*b*]thienylacetate and a number of its derivatives have been synthesized similarly [Eq. (6)].^{143, 299, 310-313}

Cyclization of the (aryltio)acetaldehydes PhSCHRCHO (R = Me, Et, or Ph) with phosphorus pentoxide gives the corresponding 2-substituted benzo[*b*]thiophene in 65–80% yield.³¹⁴

³⁰⁷ J. E. Banfield, W. Davies, N. W. Gamble, and S. Middleton, *J. Chem. Soc.* 4791 (1956).

³⁰⁸ B. D. Tilak, L. J. Pandya, T. S. Murthy, and V. S. Palkar, *4th Ann. Rept. Res., Petrol. Res. Fund, Am. Chem. Soc.* 19 (1960).

³⁰⁹ T. S. Murthy and B. D. Tilak, *J. Sci. Ind. Res. (India)* **19B**, 395 (1960).

³¹⁰ F. Sauter and P. Stütz, *Monatsh. Chem.* **98**, 1962 (1967).

³¹¹ F. Sauter and A. Barakat, *Monatsh. Chem.* **98**, 2393 (1967).

³¹² R. D. Schuetz, G. P. Nilles, and R. L. Titus, *J. Org. Chem.* **33**, 1556 (1968).

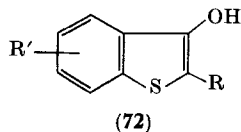
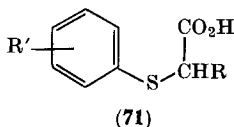
³¹³ F. Sauter and F. Ecker, *Monatsh. Chem.* **99**, 610 (1968).

³¹⁴ L. Vio, *Compt. Rend.* **257**, 459 (1963).

^{314a} G. D. Gal'pern, I. U. Numanov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **7**, 34 (1964); *Chem. Abstr.* **62**, 6450 (1965).

^{314b} I. U. Numanov, I. M. Nasyrov, G. D. Gal'pern, and A. B. Zegel'man, *Dokl. Akad. Nauk Tadzh. SSR* **8**, 26 (1965); *Chem. Abstr.* **64**, 3452 (1966).

^{314c} R. Royer, P. Demerseman, J.-P. Lechartier, A.-M. Laval-Jeantet, A. Cheutin, and M.-L. Desvoye, *Bull. Soc. Chim. France* 315 (1964).

D. CYCLIZATION OF *S*-ARYLTHIOGLYCOLIC ACIDS

Thioindoxyls (**72**) may be obtained by cyclization of the appropriate *S*-arylthioglycolic acid (**71**) with phosphorus pentoxide (yields are often low³¹⁵), hydrofluoric acid,^{106, 316} or chlorosulfonic acid,^{317, 318} (method a); Friedel-Crafts cyclization of the corresponding acid chloride (preferably prepared using thionyl chloride³¹⁹) (method b) is, however, the preferred procedure (Table V). *Meta*-substituted *S*-arylthioglycolic acids afford mixtures of 4- and 6-substituted thioindoxyls.³²⁰

Diphenyl-4,4'-dithioglycolic acid (**73**),³²¹ diphenylmethane-4,4'-dithioglycolic acid (**75a**),³²² diphenyl ether-4,4'-dithioglycolic acid

³¹⁵ G. M. Badger, D. J. Clark, W. Davies, K. T. H. Farrer, and N. P. Kefford, *J. Chem. Soc.* 2624 (1957).

³¹⁶ O. Dann and M. Kokorudz, *Chem. Ber.* **86**, 1449 (1953).

³¹⁷ Ciba Ltd., British Patent 692,962 (1953); *Chem. Abstr.* **48**, 1697 (1954).

³¹⁸ J. Mueller, U.S. Patent 2,735,853 (1956); *Chem. Abstr.* **50**, 8218 (1956).

³¹⁹ R. Mory, E. Stöcklin, and M. Schmid, U.S. Patent 2,914, 539 (1959); *Chem. Abstr.* **54**, 6759 (1960).

^{319a} P. C. Dutta and D. Mandal, *J. Indian Chem. Soc.* **31**, 827 (1954).

³²⁰ See, e.g., L. H. Werner, D. C. Schroeder, and S. Ricca, *J. Am. Chem. Soc.* **79**, 1675 (1957).

^{320a} S. K. Guha and J. N. Chatterjea, *J. Indian Chem. Soc.* **30**, 379 (1953).

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^{320d} A. K. Sinha, *J. Indian Chem. Soc.* **31**, 463 (1954).

^{320e} N. S. Dokunikhin and Yu. E. Gerasimenko, *Zh. Obshch. Khim.* **30**, 1987 (1960); *Chem. Abstr.* **55**, 7845 (1961).

^{320f} S. K. Guha, J. N. Chatterjea, and A. K. Mitra, *Chem. Ber.* **94**, 2295 (1961).

^{320g} S. K. Guha, J. N. Chatterjea, and A. K. Mitra, *Chem. Ber.* **92**, 2771 (1959).

^{320h} N. S. Dokunikhin and Yu. E. Gerasimenko, *Zh. Obshch. Khim.* **31**, 219 (1961); *Chem. Abstr.* **55**, 19247 (1961).

³²⁰ⁱ N. S. Dokunikhin and Yu. E. Gerasimenko, *Zh. Obshch. Khim.* **31**, 1927 (1961); *Chem. Abstr.* **55**, 24018 (1961).

^{320j} R. F. M. Sureau and G. R. H. Mingasson, French Patent 1,174,032 (1959); *Chem. Abstr.* **55**, 3074 (1961).

³²¹ P. C. Dutta and D. Mandal, *J. Indian Chem. Soc.* **32**, 339 (1955).

³²² P. C. Dutta and D. Mandal, *J. Indian Chem. Soc.* **32**, 497 (1955).

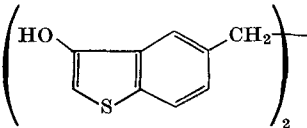
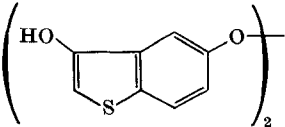
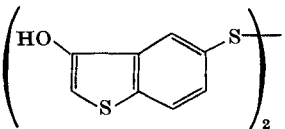
TABLE V

THIOINDOXYLS (3-HYDROXYBENZO[*b*]THIOPHENES) BY CYCLIZATION OF *S*-ARYLTHIOGLYCOLIC ACIDS

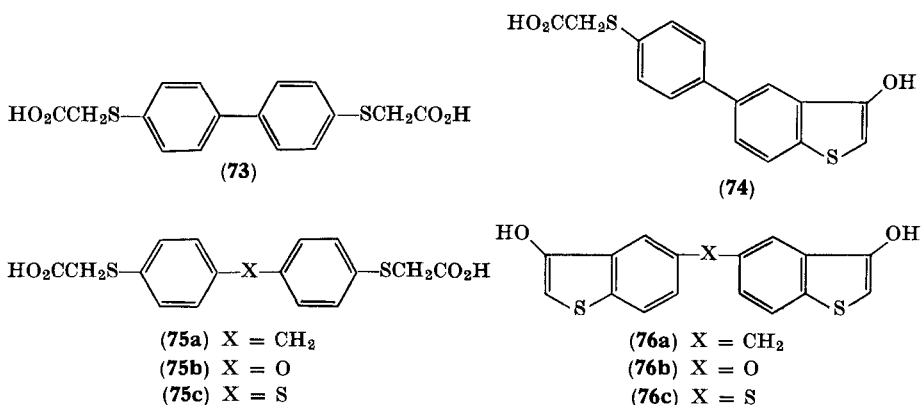
Substituents	Melting point and/or boiling point (°C)	Yield (%)	Method ^a	Ref.
None	71	100	a	316
2-Me	39–42 ^b	75–80	c	182
5-Me	101–102	64, ?, 25	a, b, b	316, 320, 625
6-Me	88–90	69	b	585
2-Et	(166–168/14 mm)	65, 62	c	281, 222
5-Ph	115	?	b	319a
5-Br	116	90, 65, 16, ?	c, d, a, b, b	315, 320, 320a
6-Br	153	?, 60	b	320, 315
4-Cl	117–118.5	?	c	320b
5-Cl	98–100	ca. 100, ?, ?, ?	b, b, c, b	117, 320, 494, 319
6-Cl	143–145	59, ?, 100	c, c, b	320c, 241, 319
7-Cl	?	?	b	320
4-Cl)	90–92	15	b	320
6-Cl)	140–145	34		
5-I	140–141	?	c	320d
7-I	151–152.5	37.5	b	320e
5-F	?	?	b	320
6-F	?	?	b	320
4,5-Cl ₂	?	?	b	320
5,6-Cl ₂	?	?	b	319, 320
5,6,7-Cl ₃	?	100	a	316
7-Me, 5-Br	?	?	a, b	106
5-Me, 6-Cl	?	100	b	319
7-Me, 5-Cl	?	?	b	319

4-Me, 5,7-Cl ₂	?	100	b	319
4,7-Me ₂ , 5-Cl	140-142 (dec.)	97, ?, ?	a, a, b	316, 317, 319
6-Br, 5-OMe	213-214	?	b	318
6-Br, 5-OEt	151-152	?	b	318
6-Cl, 5-OMe	195	?	a, b	318
6-Cl, 5-OEt	139	?	b	318
5-NHAc	130 ^b	?	c	494
5-NO ₂	155-156.5 ^b	95, 70	c	546, 494
6-NO ₂	101-101.5 ^b	97, ?	c	546, 494
7-NO ₂ , 2-CO ₂ H	160	?	c	546, 494
4-OMe	114.5	13.5	c	320f
5-OMe	119	8	c	320f
	103	1-1.5	a	320g
6-OMe	117	60-90	a	42
7-OMe	99-100	3-4	a	320f
5-OEt	104-105	60.5	c	320h
7-CO ₂ H	310	90	b	315
5-SO ₂ Me	131-132	56	c	320i
6-SO ₂ Me	141-142	83.5	c	320i
5-SO ₂ NH ₂ , 2-CO ₂ H	?	?	c	320j
5-SO ₂ NEt ₂ , 2-CO ₂ H	183-184	?	c	320j
5-SO ₂ NHPr ^t , 2-CO ₂ H	227-228	?	c	320j
5-C ₆ H ₄ SCH ₂ CO ₂ H- <i>p</i>	189-203	?	b	321
2-COC ₆ H ₄ CMe ₃ - <i>p</i>	93	?	c	272
2-COC ₆ H ₄ F- <i>p</i>	115	?	c	272
2-COC ₆ H ₄ Cl- <i>p</i>	150	?	c	272
2-COC ₆ H ₄ OMe- <i>p</i>	112	?	c	272
2-COC ₆ H ₄ OEt- <i>p</i>	140	?	c	272
6-Me, 2-COC ₆ H ₅	105	?	c	272
5-Me, 2-COC ₆ H ₄ OEt- <i>p</i>	140	?	c	272
5,6-Me ₂ , 2-COC ₆ H ₄ OEt- <i>p</i>	177	?	c	272
5-Cl, 2-COC ₆ H ₄ OEt- <i>p</i>	154	?	c	272

TABLE V—*continued*

Substituents	Melting point and/or boiling point (°C)	Yield (%)	Method ^a	Ref.
7-Cl, 2-COC ₆ H ₄ OEt- <i>p</i>	134	?	c	272
5-OMe, 2-COC ₆ H ₄ OEt- <i>p</i>	150	?	c	272
	Yellow solid, very susceptible to oxidation	—	b	322
	Very susceptible to oxidation	—	b	323
	Very susceptible to oxidation	—	b	324

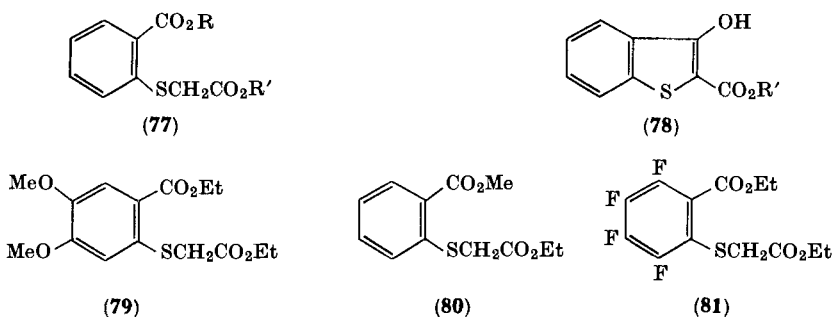
^a See text for discussion of methods.^b Isolated as its acetate (melting point given).



(75b),³²³ and diphenyl thioether-4,4'-dithioglycolic acid (75c)³²⁴ cyclize normally to give **74**, **76a**, **76b**, and **76c**, respectively.

S-Arylthioglycolic acids possessing an *ortho* carboxyl group (77; R = R' = H) are cyclized by acetic anhydride or base to the corresponding thioindoxyl-2-carboxylic acids (78; R' = H) (method c), which often lose carbon dioxide spontaneously to give the thioindoxyls (Table V).³¹⁵ *S*-(*o*-Cyanophenyl)thioglycolic acids give similar products on treatment with alkali (method d) (Table V).³¹⁵

A large number of thioindoxyls had been prepared by the above methods prior to 1952; a full account of this work has been given elsewhere.³²⁵



³²³ P. C. Dutta and D. Mandal, *J. Indian Chem. Soc.* **33**, 54 (1956).

³²⁴ P. C. Dutta and D. Mandal, *J. Indian Chem. Soc.* **33**, 812 (1956).

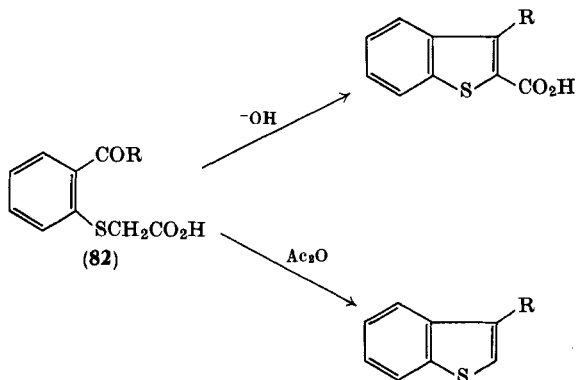
³²⁵ H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 67. Wiley (Interscience), New York, 1954.

Cyclization of the diesters (**79** and **80**) with sodium in toluene³²⁶ and sodium methoxide,¹⁴⁸ respectively, affords the corresponding 2-(ethoxycarbonyl)thioindoxyls; the ester (**81**) cyclizes similarly on treatment with sodium hydride to give 2-ethoxycarbonyl-4,5,6,7-tetrafluorothioindoxyl.¹⁰⁹

Thioindoxyl-1,1-dioxide,³²⁷ 2-(*p*-nitrophenyl)thioindoxyl,³²⁸ and various substituted 2-(aroyl)thioindoxyls²⁷² may be prepared by analogous procedures.

Thioindoxyls are generally obtained in good yields by the above routes, but precautions must be taken to minimize the several possible side reactions: oxidation of the thioindoxyl to a thioindigo dye, intermolecular condensation [as demonstrated by the formation of (*p*-acetylphenylthio)acetic acid from *S*-phenylthioglycolic acid³¹⁶], or fission of the carbon-sulfur bond (minimized by the use of basic cyclizing agents) may occur.²⁹¹

The synthesis of 3-alkyl- and 3-arylbenzo[*b*]thiophenes, developed by an Italian group,³²⁹⁻³³⁴ involves the cyclization of *o*-acyl-*S*-



SCHEME 2

³²⁶ D. G. Bew and G. R. Clemo, *J. Chem. Soc.* 1314 (1953).

³²⁷ M. Regitz, *Chem. Ber.* **98**, 36 (1965).

³²⁸ F. Gialdi, R. Ponci, and A. Baruffini, *Farmaco (Pavia), Ed. Sci.* **15**, 856 (1960).

³²⁹ A. Ricci, *Ann. Chim. (Rome)* **43**, 323 (1953).

³³⁰ C. Finzi, C. Angelini, and G. Grandolini, *Ann. Chim. (Rome)* **45**, 54 (1955).

³³¹ A. Ricci and N. Cagnoli, *Ann. Chim. (Rome)* **45**, 172 (1955).

³³² N. Cagnoli, A. Ricci, and N. Fedi, *Ann. Chim. (Rome)* **47**, 606 (1957).

³³³ C. Angelini, *Ann. Chim. (Rome)* **47**, 705 (1957).

³³⁴ C. Angelini, *Ann. Chim. (Rome)* **48**, 637 (1958).

TABLE VI
BENZO[*b*]THIOPHENES BY CYCLIZATION OF
S-(*o*-ACYL)ARYLTHIOGLYCOLIC ACIDS

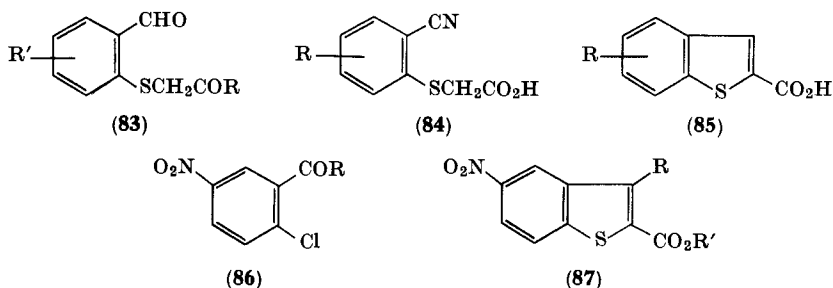
Substituents	Melting point and/or boiling point (°C)	Yield (%)	Method ^a	Ref.
3-Me	(112–113/10 mm)	?	a	329
3-Me, 5-NH ₂	51–52	?	a	331
3,6-Me ₂ , 5-NO ₂	131	?	a	330
3-Ph, 5-NO ₂	156–157	?	a	333
3-Ph, 5-NHAc	128–129	?	a	333
3-Me, 2-CO ₂ H	239–240	?	a	329
3,5-Me ₂ , 2-CO ₂ H	263–264 (dec.)	100	a	625
3,4(or 3,6)-Me ₂ , 2-CO ₂ H	261–262 (dec.)	90	a	625
3-Me, 5-NH ₂ , 2-CO ₂ H	267–268	?	a	331
3,6-Me ₂ , 5-NO ₂ , 2-CO ₂ H	312–313 (dec.)	80	a	330
3,6-Me ₂ , 5-NH ₂ , 2-CO ₂ H	271 (dec.)	90	a	330
3-Me, 5-CNS, 2-CO ₂ H	232–233	?	a	332
3-Me, 5-SCH ₂ CO ₂ H, 2-CO ₂ H	274–275	40	a	332
3-Ph, 5-NO ₂ , 2-CO ₂ H	250–251	?	a	185, 333
3-Ph, 5-NH ₂ , 2-CO ₂ H	219–220	?	a	333
3-Ph, 5-NHAc, 2-CO ₂ H	234	?	a	333
3-Ph, 5,7-(NO ₂) ₂ , 2-CO ₂ H	252–253	?	a	334
5-Br, 2-CO ₂ H	235	48	b	315
5-NO ₂ , 2-CO ₂ H	238–240	33	a	538
2-CO ₂ H	236	20	b	315

^a For a discussion see text.

phenylthioglycolic acids (**82**; R = alkyl or aryl) either with acetic anhydride to give the required benzo[*b*]thiophene, or with dilute alkali, which affords the corresponding 2-carboxylic acid (method a) (Scheme 2) (Table VI). Analogous basic cyclization of the aldehydes (**83**; R = OH) or reductive cyclization (Stephen's procedure) of the corresponding nitriles (**84**) (method b) gives the corresponding 2-carboxylic acids (**85**) (Table VI).³¹⁵ Similar cyclization of the aldehydes (**83**; R = alkyl) affords the corresponding 2-acylbenzo[*b*]thiophenes.³³⁵

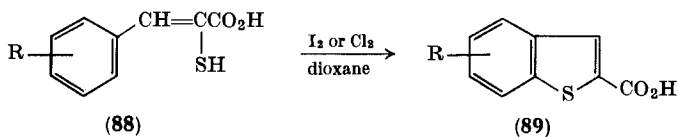
Treatment of the aldehyde (**86**; R = H) with ethyl thioglycolate and sodium ethoxide provides an elegant single-stage synthesis of the otherwise rather inaccessible ethyl 5-nitrobenzo[*b*]thiophene-2-

³³⁵ M. Martynoff, *Compt. Rend.* **234**, 736 (1952).



carboxylate (**87**; R = H, R' = Et) (85%).^{218, 336, 337} The 3-methyl derivative (**87**; R = Me, R' = Et) is obtained analogously from the ketone (**86**; R = Me).²⁹⁸ Alternatively, **87** (R = R' = H) may be prepared by treating **86** (R = H) and thioglycolic acid with an excess of sodium hydroxide.³³⁸ When ethanolic 2-benzoyl-4,6-dinitrochlorobenzene and thioglycolic acid are heated in the presence of base, 3-phenyl-5,7-dinitrobenzo[*b*]thiophene-2-carboxylic acid is obtained.³³⁴

E. CYCLIZATION OF β -ARYL- α -MERCAPTOACRYLIC ACIDS AND RELATED COMPOUNDS



Condensation of an aromatic aldehyde with rhodanine affords the corresponding 5-benzylidenerhodanine, which gives a β -aryl- α -mercaptoacrylic acid (**88**) on alkaline hydrolysis.³³⁹ In 1956, Campaigne and Cline³³⁹ found that the acids **88**, or the corresponding disulfides, could be cyclized in variable yields (Table VII) to give the corresponding benzo[*b*]thiophene-2-carboxylic acids (**89**) by heating them with iodine in dioxane or nitrobenzene. Recently, chlorine has been found to be a more efficient cyclizing agent than iodine.³⁴⁰ Ring

³³⁶ N. B. Chapman, K. Clarke, and S. D. Saraf, *J. Chem. Soc., C* 731 (1967).

³³⁷ M. Martin-Smith, W. E. Sneader, I. Brown, and S. T. Reid, *J. Chem. Soc., C* 1899 (1967).

³³⁸ A. Mustafa, S. M. A. D. Zayed, and A. Emran, *Ann. Chem.* **704**, 176 (1967).

³³⁹ E. Campaigne and R. E. Cline, *J. Org. Chem.* **21**, 39 (1956).

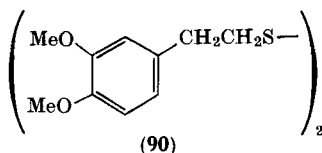
³⁴⁰ P. M. Chakrabarti, University of Hull, unpublished results (1968).

TABLE VII
BENZO[*b*]THIOPHENE-2-CARBOXYLIC ACIDS BY CYCLIZATION OF
 β -ARYL- α -MERCAPTOACRYLIC ACIDS (88 \rightarrow 89)

Substituents	Melting point (°C)	Yield (%)	Ref.
None	240–241	68	339
4-Br	272	50–55	344
5-OH	?	?	342
3-Me, 5-OH	254–255 (dec.)	88	343
5-OMe	215–216	40	341
6-OMe	251	7.5	341
4,5-(OMe) ₂	240–241	30	189
5,6-(OMe) ₂	260–261	25	339
5,6-(OEt) ₂	245–246	31	341
5,6-Methylenedioxy	290–291	62	189
5,6,7-(OMe) ₃	180–181	37	341

closure is facilitated by electron-releasing groups (e.g., OH, OR) at the *meta* position of the mercaptoacrylic acid,^{189, 339, 341–343} although 4-bromobenzo[*b*]thiophene-2-carboxylic acid has been prepared from β -(*o*-bromophenyl)- α -mercaptoacrylic acid.³⁴⁴ β -(*p*-Ethoxyphenyl)- and β -(2,4-dimethoxyphenyl)- α -mercaptoacrylic acid afford only tars.³⁴¹

Pentafluoro-, 2,3,5,6-, 2,3,4,6- and 2,3,4,5-tetrafluorobenzaldehyde readily form benzylidene derivatives with rhodanine.¹¹⁰ The products are hydrolyzed by base to β -aryl- α -mercaptoacrylic acids, which cannot be isolated, but which spontaneously cyclize by nucleophilic displacement of fluorine to give 4,5,6,7-tetrafluoro- and 4,5,7-, 4,6,7- and 5,6,7-trifluorobenzo[*b*]thiophene-2-carboxylic acid, respectively.



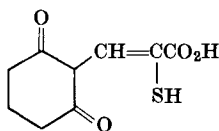
³⁴¹ E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.* **26**, 1326 (1961).

³⁴² E. S. Neiss, M.S. Thesis, Indiana University (1963).

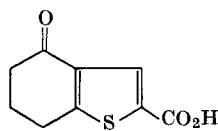
³⁴³ E. Campaigne, T. Bosin, and E. S. Neiss, *J. Med. Chem.* **10**, 270 (1967).

³⁴⁴ P. Faller, *Bull. Soc. Chim. France* 3667 (1966).

Treatment of the disulfide (90) with iodine in dioxane under various conditions gives low yields of 5,6-dimethoxy-2,3-dihydrobenzo[*b*]-thiophene.³⁴⁵ At high temperatures in ethylene glycol a mixture of this compound and the dehydrogenated product, 5,6-dimethoxybenzo[*b*]thiophene, is obtained. These observations demonstrate the importance of the double bond in the side chain of the mercaptoacrylic acids (88) in promoting their cyclization.



(91)



(92)

In a closely related reaction, heating the trimethylamine salt of the condensation product of dihydroresorcinol and 5-ethoxymethylene-3-methylrhodanine with aqueous alkali affords 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one-2-carboxylic acid (92), via the intermediate (91).³⁴⁶

F. KROLLPFEIFFER SYNTHESSES

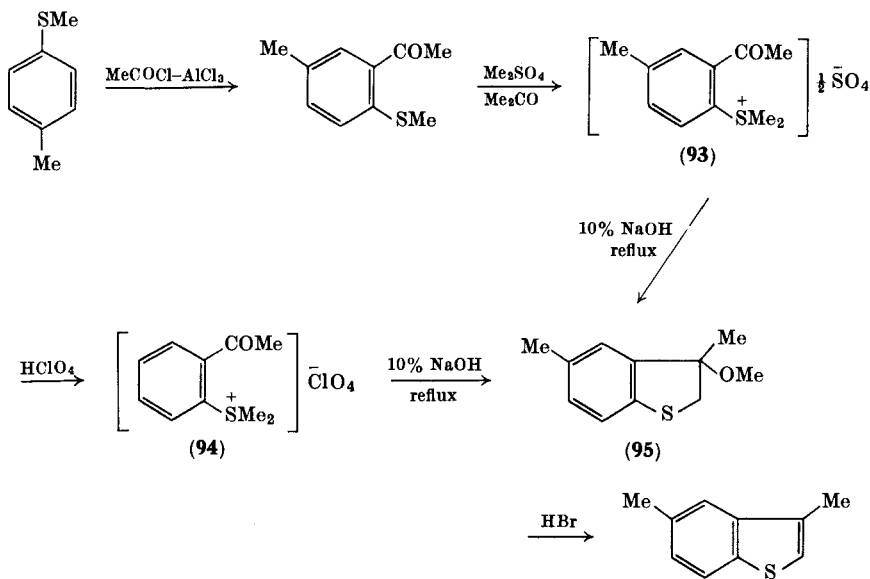
A modification by Guerra³⁴⁷ of a Krollpfeiffer³⁴⁸ synthesis [the cyclization, and dealkylation, of (*o*-acylphenyl)dialkyl sulfonium salts] allows 3,5-dimethylbenzo[*b*]thiophene to be obtained in improved yield from methyl *p*-tolyl sulfide (Scheme 3). Isolation of the crystalline salt (93), and use of hydrogen bromide in the final stage, improves Krollpfeiffer's yield of 70% to 83–93%. Alternatively, treatment of the sulfonium salt (93) with perchloric acid gives the perchlorate salt (94), which affords 95 on treatment with base. A series of 5-methyl-3-benzo[*b*]thienylcarboxylic acids has been prepared analogously [Eq. (7)].³⁴⁷ In these cases, the final stage shown in Scheme 3 can be eliminated, since the intermediates related to 95 lose hydrogen bromide spontaneously.

³⁴⁵ E. Campaigne and B. G. Heaton, *J. Org. Chem.* **29**, 2372 (1964).

³⁴⁶ H. Behringer and K. Falkenberg, *Chem. Ber.* **99**, 3309 (1966).

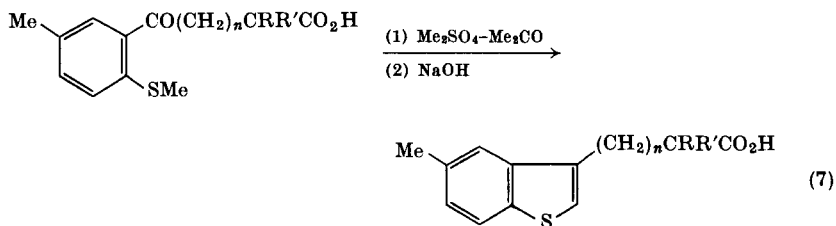
³⁴⁷ R. A. Guerra, *Acta Salmanticensia, Ser. Cienc.* [N.S.] **6**, 7 (1963); *Chem. Abstr.* **63**, 5581 (1965).

³⁴⁸ H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), pp. 36 and 70. Wiley (Interscience), New York, 1954.



SCHEME 3

2-Carboxybenzo[b]thiophenes (**97**; R = Ph, R' = 5-Cl³⁴⁹; R = C₆H₄CO₂H-*o*, R' = 5-Cl³⁴⁹; R = C₆H₄CO₂H-*o*, R' = 5-Me³⁵⁰; R = α-thienyl, R' = 5-Cl³⁴⁹; R = CH₂CH₂CO₂H, R' = 5-Me^{348, 351}; R = CH₂CH₂CO₂H, R' = 5-Cl³⁵¹) may be prepared by treatment of the sulfides (**96**) with chloroacetic acid as shown in Scheme 4. Similarly, a mixture of **99** and **100** has been prepared from **98**,³⁵² and **101** affords **102**.³⁵³



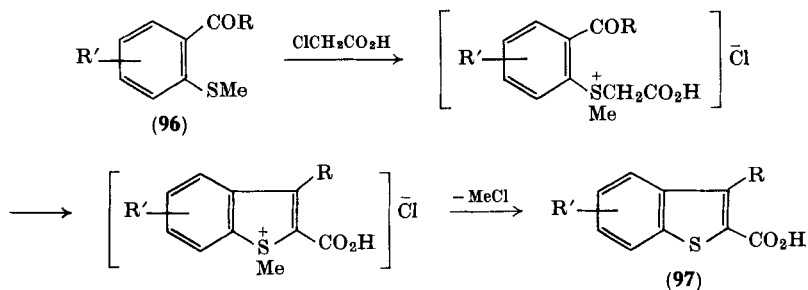
³⁴⁹ R. D. Schuetz and L. Ciporin, *J. Org. Chem.* **23**, 206 (1958).

³⁵⁰ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 132. Wiley (Interscience), New York, 1954.

³⁵¹ F. Sauter and P. Stütz, *Monatsh. Chem.* **99**, 715 (1968).

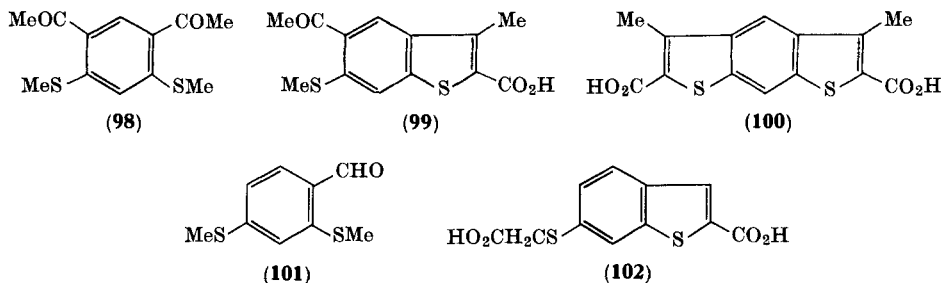
³⁵² A. Martani, *Gazz. Chim. Ital.* **90**, 1213 (1960).

³⁵³ A. Martani and O. Roussel, *Ann. Chim. (Rome)* **57**, 121 (1967).

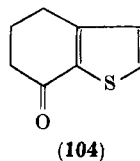
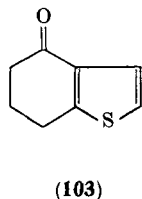


SCHEME 4

6-(Methylthio)thioindoxyl has been prepared by treatment of thioresorcinol dimethyl ether with chloroacetyl chloride and aluminum chloride.³⁵²



G. FROM THIOPHENES



The above methods for the synthesis of benzo[b]thiophenes involve the fusion of a thiophene ring on to an already existing benzene ring. The alternative approach, i.e., that of building a benzene ring on to a thiophene ring, also has important applications.

4,5,6,7-Tetrahydrobenzo[b]thiophen-4-one (**103**) may be prepared from γ -(2-thienyl)butyric acid by cyclization with phosphoric acid³⁵⁴ or by Friedel-Crafts cyclization of the corresponding acid chloride.^{194, 355, 356} Its 5-methyl,³⁵⁷ 2-ethyl,¹⁹⁴ 2-isopropyl,³⁵⁸ 2- and 3-*tert*-butyl,³⁵⁹ 2,3-dimethyl,³⁶⁰ 2-ethyl-3-methyl,³⁶⁰ and 2-bromo³⁵⁴ derivatives and diethyl 4,5,6,7-tetrahydrobenzo[b]thiophene-4,5-dicarboxylate³⁶¹ may be prepared similarly. 4,5,6,7-Tetrahydrobenzo[b]thiophen-7-one (**104**)^{357, 362, 363} and its 5- and 6-methyl³⁵⁷ and 2-chloro³⁶² derivatives are obtained from the appropriately substituted γ -(3-thienyl)butyric acid. A recent patent³⁶⁴ describes the vapor phase cyclization of γ -(2-thienyl)butyric acid to **103**. Ketones (**103** and **104**) are useful intermediates for the synthesis of 4- and 7-substituted benzo[b]thiophenes, respectively; their reactions are discussed in Section VI, B, 4.

A patent³⁶⁵ describes the high temperature catalytic cyclization of 2-butenylthiophene to benzo[b]thiophene.

Successive hydrolysis and dehydrogenation of the adduct of 2-vinylthiophene with maleic anhydride gives benzo[b]thiophene-4,5-dicarboxylic anhydride.^{366, 367}

Benzo[b]thiophene is a minor product of the pyrolysis of thiophene.³⁶⁸⁻³⁷⁰ Three mechanisms have been advanced for its forma-

³⁵⁴ S. Nishimura, M. Nakamura, M. Suzuki, and E. Imoto, *Nippon Kagaku Zasshi* **83**, 343 (1962); *Chem. Abstr.* **59**, 3862 (1963).

³⁵⁵ M. C. Kloetzel, J. E. Little, and D. M. Frisch, *J. Org. Chem.* **18**, 1511 (1953).

³⁵⁶ M. Maillat and M. Sy, *Compt. Rend.* **C264**, 1193 (1967).

³⁵⁷ P. Cagniant and G. Merle, *Compt. Rend.* **C266**, 1784 (1968).

³⁵⁸ S. F. Bedell, E. C. Spaeth, and J. M. Bobbitt, *J. Org. Chem.* **27**, 2026 (1962).

³⁵⁹ M. Sy, Ng. Ph. Buu-Hoï, and Ng. D. Xuong, *J. Chem. Soc.* 21 (1955).

³⁶⁰ J. Lamy, D. Lavit, and Ng. Ph. Buu-Hoï, *J. Chem. Soc.* 4202 (1958).

³⁶¹ R. Wilputte and R. H. Martin, *Bull. Soc. Chim. Belges* **65**, 874 (1956).

³⁶² B. P. Fabrichnyi, I. F. Shalavina, S. E. Zurabyan, Ya. L. Gol'dfarb, and S. M. Kostrova, *Zh. Organ. Khim.* **4**, 680 (1968).

³⁶³ D. W. H. MacDowell and T. D. Greenwood, *J. Heterocyclic Chem.* **2**, 44 (1965).

³⁶⁴ Mobil Oil Corp., Netherlands Patent Appl. 6,601,732 (1966); *Chem. Abstr.* **66**, 46323 (1967).

³⁶⁵ K. L. Kreuz, U.S. Patent 2,686,185 (1954).

³⁶⁶ J. F. Scully and E. V. Brown, *J. Am. Chem. Soc.* **75**, 6329 (1953).

³⁶⁷ W. Davies and Q. N. Porter, *J. Chem. Soc.* 4958 (1957).

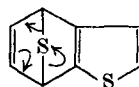
³⁶⁸ E. K. Fields and S. Meyerson, *Chem. Commun.* 708 (1966).

³⁶⁹ E. K. Fields and S. Meyerson, in "Organosulfur Chemistry" (M. J. Janssen, ed.), Chapter 8, p. 143. Wiley (Interscience), New York, 1967.

³⁷⁰ E. K. Fields and S. Meyerson, *Am. Chem. Soc. Div. Petrol. Chem., Preprints* **12**, 57 (1967).



(105)



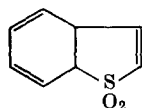
(106)

tion³⁶⁸⁻³⁷²; the most probable involves the formation of thiophene (105) by intramolecular dehydrogenation, followed by its reaction with thiophene and extrusion of sulfur from the adduct (106).³⁶⁸⁻³⁷⁰ Benzo[*b*]thiophene and its 4,5,6,7-tetrachloro and 4,5,6,7-tetraphenyl derivatives are minor products of the pyrolysis in thiophene of phthalic anhydride and its tetrachloro and tetraphenyl derivatives, respectively.³⁶⁸⁻³⁷⁰

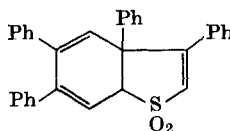
H. BENZO[*b*]THIOPHENE-1,1-DIOXIDES

1. From Thiophene-1,1-dioxides

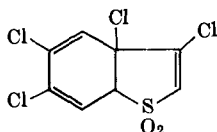
Thiophene-1,1-dioxide,³⁷³ and its 3,4-diphenyl derivative³⁷⁴ undergo Diels-Alder reactions in which they behave both as diene and



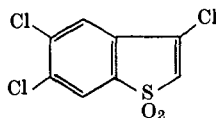
(107)



(108)



(109)



(110)

dienophile. The unstable dimers lose sulfur dioxide to give 3a,7a-dihydrobenzo[*b*]thiophene-1,1-dioxide (107) and 3,3a,5,6-tetraphenyl-3a,7a-dihydrobenzo[*b*]thiophene-1,1-dioxide (108), respectively. A

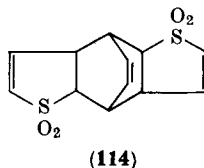
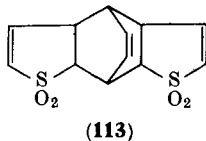
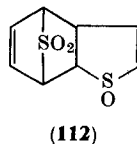
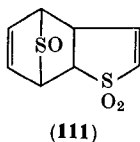
³⁷¹ H. Wynberg and A. Bantjes, *J. Org. Chem.* **24**, 1421 (1959).

³⁷² C. D. Hurd, A. R. Macon, J. I. Simon, and R. V. Levetan, *J. Am. Chem. Soc.* **84**, 4509 (1962).

³⁷³ W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.* **76**, 1936 (1954).

³⁷⁴ C. G. Overberger and J. M. Whelan, *J. Org. Chem.* **26**, 4328 (1961).

similar product (**109**) is probably formed from 3,4-dichlorothiophene-1,1-dioxide,³⁷⁵ but it readily loses hydrogen chloride to give, *inter alia*, 3,5,6-trichlorobenzo[*b*]thiophene-1,1-dioxide (**110**).



Oxidation of thiophene with perbenzoic acid,^{373, 376} or peracetic acid,^{377, 378} affords the adduct (**111**), or its isomer (**112**) (the available evidence supports structure **111**^{377, 378}), by a Diels–Alder reaction between the intermediates thiophene-1,1-dioxide and thiophene-1-oxide. Similar reactions have been observed with substituted thiophenes.³⁷⁶ When a solution of thiophene-1,1-dioxide is allowed to stand, the adduct (**113**), or its isomer (**114**), is formed.^{373, 378}

Treatment of 3,4-dichlorosulfolane with ammonia affords 3a,7a-dihydrobenzo[*b*]thiophene-1,1-dioxide (**107**) as the major product, together with **113**.^{379, 380} 3,4-Dibromosulfolane behaves analogously on treatment with pyridine.^{373, 378}

3,4-Dichlorothiophene-1,1-dioxide undergoes Diels–Alder reactions with butadiene and isoprene to give mixtures of **115a** and **116a** and

³⁷⁵ H. Bluestone, R. Bimber, R. Berkey, and Z. Mandel, *J. Org. Chem.* **26**, 346 (1961).

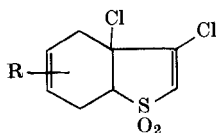
³⁷⁶ J. L. Melles and H. J. Backer, *Rec. Trav. Chim.* **72**, 491 (1953).

³⁷⁷ W. Davies, N. W. Gamble, F. C. James, and W. E. Savage, *Chem. Ind. (London)* 804 (1952).

³⁷⁸ H. J. Backer and J. L. Melles, *Koninkl. Ned. Akad. Wetenschap., Proc.* **54B**, 340 (1951); *Chem. Abstr.* **47**, 6932 (1953).

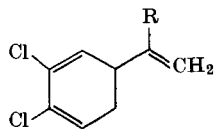
³⁷⁹ J. E. Mahan, U.S. Patent 2,786,851 (1957); *Chem. Abstr.* **51**, 12146 (1957).

³⁸⁰ M. Procházka and V. Horák, *Collection Czech. Chem. Commun.* **24**, 2278 (1959).



(115a) R = H

(115b) R = Me (5- and 6-isomers)

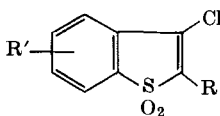
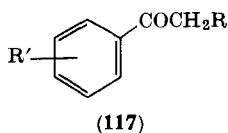


(116a) R = H

(116b) R = Me

115b and **116b**, respectively.^{229, 375} Butadiene and 2,3-dihydrothiophene-1,1-dioxide similarly afford 2,3,3a,4,7,7a-hexahydrobenzo[b]thiophene-1,1-dioxide.²⁷

2. By Chlorosulfonation of Acetophenone Derivatives



(118a) R = Me, R' = 6-Cl

(118b) R = Me, R' = H

(118c) R = CH₂NMe₂, R' = H(118d) R = CH₂N(CH₂)₄O, R' = H

Meyer³⁸¹ has noted that homologs of acetophenone (**117**) undergo cyclization during chlorosulfonation reactions to give 2-substituted 3-chlorobenzo[b]thiophene-1,1-dioxides (**118**). Thus, with chlorosulfonic acid at 100°, *p*-chloropropiophenone affords 3,6-dichloro-2-methylbenzo[b]thiophene-1,1-dioxide (**118a**). The chlorosulfonation of propiophenone itself to give **118b** is more difficult to achieve, but two Mannich bases of acetophenone readily cyclize under these conditions to give the 2-aminomethyl-3-chlorobenzo[b]thiophene-1,1-dioxide derivatives (**118c** and **118d**).

V. Miscellaneous Reactions and Properties of Benzo[b]thiophenes

In this section the reactions of benzo[b]thiophene and its derivatives which do not fall conveniently into any of the subsequent sections are reviewed.

³⁸¹ R. F. Meyer, *J. Heterocyclic Chem.* **3**, 174 (1966).

A number of color reactions of benzo[b]thiophene have been described.^{382, 383}

When either indole or benzofuran is passed with hydrogen sulfide over an alumina catalyst, partial conversion into benzo[b]thiophene occurs.³⁸⁴ Benzo[b]thiophene and ammonia similarly afford indole.

With alkaline potassium permanganate and other oxidizing agents benzo[b]thiophene gives *o*-carboxybenzenesulfonic acid,³⁸⁵ and 3-methylbenzo[b]thiophene affords maleic acid on catalytic aerobic oxidation.³⁸⁶

With chromium tricarbonyl³⁸⁷ and with either triirondodecacarbonyl³⁸⁷⁻³⁸⁹ or iron pentacarbonyl³⁸⁹ benzo[b]thiophene affords a yellow complex, $C_8H_6S \cdot Cr(CO)_3$, and a red-orange complex, $C_8H_6S \cdot Fe_2(CO)_6$, respectively.

2-Triphenylsilyl-³⁹⁰ and 2- and 3-trimethylsilylbenzo[b]thiophene^{391, 392} have been prepared, and their rates of cleavage by acids and bases measured. The reaction between 2-benzo[b]thienyltrichlorosilane and *p*-bromophenyl methyl sulfide in the presence of sodium gives 2-[tri(*p*-methylthiophenyl)silyl]benzo[b]thiophene.³⁹³

Hydrolysis of the product from the reaction between 2-benzo[b]thienyllithium and methyl borate with acid is said to give 2-benzo[b]thienylboronic acid.³⁹⁴

It is claimed that benzo[b]thiophene reacts with hexafluorophosphoric acid in liquid sulfur dioxide, or with a mixture of anhydrous hydrofluoric acid and phosphorus pentafluoride, to give "solid adducts," the natures of which have not been disclosed.³⁹⁵

³⁸² C. Karr, *Anal. Chem.* **26**, 528 (1954).

³⁸³ H. D. Hartough, *Anal. Chem.* **23**, 1128 (1951).

³⁸⁴ T. Lesiak, *Roczniki Chem.* **39**, 589 (1965); *Chem. Abstr.* **63**, 16293 (1965).

³⁸⁵ F. B. Erickson, U.S. Patent 2,642,458 (1953); *Chem. Abstr.* **48**, 5219 (1954).

³⁸⁶ E. G. G. Werner, Dutch Patent 70,105 (1952); *Chem. Abstr.* **47**, 6439 (1953).

³⁸⁷ R. B. King and F. G. A. Stone, *J. Am. Chem. Soc.* **82**, 4557 (1960).

³⁸⁸ R. B. King, P. M. Treichel, and F. G. A. Stone, *J. Am. Chem. Soc.* **83**, 3600 (1961).

³⁸⁹ T. A. Manuel, *Inorg. Chem.* **3**, 1794 (1964).

³⁹⁰ R. H. Meen and H. Gilman, *J. Org. Chem.* **20**, 73 (1955).

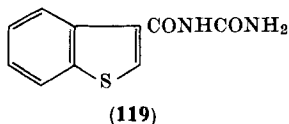
³⁹¹ C. Eaborn and J. A. Sperry, *J. Chem. Soc.* 4921 (1961).

³⁹² J. A. Sperry, U.S. Dept. Comm., Office Tech. Serv., PB Rept. **145,953** (1959); *Chem. Abstr.* **58**, 4592 (1963).

³⁹³ G. E. Schroll, U.S. Patent 2,914,548 (1959); *Chem. Abstr.* **54**, 7651 (1960).

³⁹⁴ J. Yates and R. S. Airs, British Patent 814,647 (1959); *Chem. Abstr.* **54**, 8851 (1960).

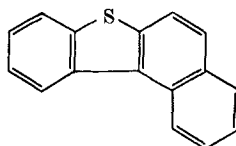
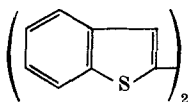
³⁹⁵ C. L. van Panthaleon van Eck and W. C. B. Smithuyzen, Dutch Patent 83,145 (1956); *Chem. Abstr.* **52**, 2392 (1958).



Benzo[*b*]thiophene reacts with biuret to give the ureide (119).³⁹⁶

A. STABILITY OF BENZO[*b*]THIOPHENE

Benzo[*b*]thiophene is best stored in amber-colored bottles or tin cans; in the presence of certain acid catalysts it polymerizes.³⁹⁷ On pyrolysis (see also Section V,C) it undergoes self-condensation less readily than indole.³⁹⁸ On exposure to daylight or mercury vapor lamp



irradiation, benzo[*b*]thiophene is believed to undergo self-condensation to give significant quantities of **120** and **121**, together with hydrogen and hydrogen sulfide.^{120, 130, 399}

B. RING-EXPANSION REACTIONS

Unlike benzofuran, pyrrole, and certain indoles,⁴⁰⁰ benzo[*b*]thiophene does not react with dichlorocarbene.^{400, 401}

The reaction between benzo[*b*]thiophene and ethyl diazoacetate affords at least three products^{228, 402}; two of these are ethyl *cis*- and *trans*-2,3-dihydrobenzo[*b*]thiophene-2,3-ylene acetate (**30**).⁴⁰² The third is believed by Badger *et al.*²²⁸ to result from attack on the benzene

³⁹⁶ D. E. Adelson, U.S. Patent 2,576,895 (1951); *Chem. Abstr.* **46**, 9588 (1952).

³⁹⁷ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 29. Wiley (Interscience), New York, 1954.

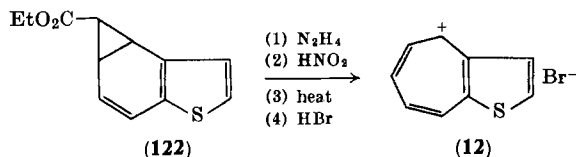
³⁹⁸ J. J. Madison and R. M. Roberts, *Ind. Eng. Chem.* **50**, 237 (1958).

³⁹⁹ W. E. Haines, G. L. Cook, and J. S. Ball, *J. Am. Chem. Soc.* **78**, 5213 (1956).

⁴⁰⁰ D. G. Hawthorne and Q. N. Porter, *Australian J. Chem.* **19**, 1751 (1966).

⁴⁰¹ W. E. Parham, C. G. Fritz, R. W. Soeder, and R. M. Dodson, *J. Org. Chem.* **28**, 577 (1963).

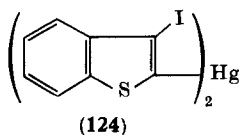
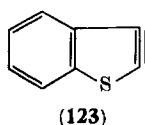
⁴⁰² G. M. Badger, B. J. Christie, H. J. Rodda, and J. M. Pryke, *J. Chem. Soc.* 1179 (1958).



ring; it may have structure **122**. In an independent investigation of the same reaction, Pettit *et al.*^{403, 404} isolated only the adduct (**122**), from which they obtained the previously unknown thienotropylium cation (**12**) by the series of reactions outlined.

C. 2,3-DEHYDROBENZO[*b*]THIOPHENE (BENZO[*b*]THIOPHYNE)

This hetaryne may have been handled in 1933 by Komppa and Weckman⁴⁰⁵ when 3-bromobenzo[*b*]thiophene was heated with ethanolic potassium hydroxide at 200° to give a mixture of starting material (4%), benzo[*b*]thiophene (65%), and thiooxindole (15%). In 1954, Brower and Amstutz⁴⁰⁶ treated 3-bromobenzo[*b*]thiophene with piperidine at 255° and obtained a mixture of benzo[*b*]thiophene and 2-piperidinobenzo[*b*]thiophene. It is possible that these reactions involve the formation of benzo[*b*]thiophyne (**123**) as an intermediate; they have not been reinvestigated so far as we are aware. However, it is more probable that they proceed via an AE_a mechanism.^{406a}



Wittig *et al.*, in a personal communication to Kauffmann,⁴⁰⁷ claim to have generated **123** from **124** by a method analogous to that used to generate thiophyne,^{408, 409} and to have trapped it with tetraphenylcyclopentadienone.

⁴⁰³ D. Sullivan and R. Pettit, *Tetrahedron Letters* 401 (1963).

⁴⁰⁴ R. G. Turnbo, D. L. Sullivan, and R. Pettit, *J. Am. Chem. Soc.* **86**, 5630 (1964).

⁴⁰⁵ G. Komppa and S. Weckman, *J. Prakt. Chem.* **138**, 109 (1933).

⁴⁰⁶ K. R. Brower and E. D. Amstutz, *J. Org. Chem.* **19**, 411 (1954).

^{406a} R. W. Hoffmann, in "Dehydrobenzene and Cycloalkynes," p. 289. Academic Press, New York, 1967.

⁴⁰⁷ T. Kauffmann, *Angew. Chem. Intern. Ed. Eng.* **4**, 554 (1965).

⁴⁰⁸ G. Wittig and V. Wahl, *Angew. Chem.* **73**, 492 (1961).

⁴⁰⁹ G. Wittig, *Angew. Chem. Intern. Ed. Eng.* **1**, 415 (1962).

Since benzo[*b*]thiophene is a product of the pyrolysis of thiophene and of the reaction between thiophene and benzyne (Section IV, G), Fields and Meyerson^{369, 370} have examined the pyrolysis of benzo[*b*]thiophene and its reaction with benzyne. The latter reaction gives rise to a complex mixture of polycyclic sulfur heterocycles, in addition to anthracene and phenanthrene. The formation of some of these products probably involves adduct formation between benzo[*b*]thiophene and benzyne, followed by subsequent reactions of the adducts. Others are possibly formed by hydrogen transfer from benzo[*b*]thiophene to benzyne, followed by dimerization of the resulting benzo[*b*]thiophyne (**123**), or by its reaction with more benzo[*b*]thiophene. In addition, insertion of benzyne into benzo[*b*]thiophene gives a mixture of phenylbenzo[*b*]thiophenes. Pyrolysis of benzo[*b*]thiophene produces a similar complex mixture of products, which may be formed by way of intramolecular dehydrogenation of the starting material to give **123**, or by way of thiophyne, which may possibly arise by cleavage of the benzo[*b*]thiophene molecule.

VI. Derivatives of Benzo[*b*]thiophene

A. ELECTROPHILIC SUBSTITUTION OF BENZO[*b*]THIOPHENE AND ITS DERIVATIVES

This section is devoted to a brief survey of the established patterns of electrophilic substitution in benzo[*b*]thiophene and its derivatives. A more detailed discussion of individual reactions is given in the appropriate subsequent section (Section VI, B–P).

Electrophilic substitution reactions of benzo[*b*]thiophene and its derivatives seldom lead to a single homogeneous product. In some cases only the major isomer has been isolated, and often its purity and precise identity are in doubt. The results are often confusing and contradictory. The earlier work should be re-examined with modern chromatographic and spectroscopic techniques to allow a meaningful rationalization of the effects of substituents on the direction of electrophilic substitution in benzo[*b*]thiophene derivatives.

1. *Benzo[*b*]thiophene*

Monosubstitution (e.g., chlorination, bromination, and Friedel–Crafts acylation) of benzo[*b*]thiophene usually gives a mixture of

the 2- and 3-isomers, in which the latter predominates. In some cases (e.g., Friedel–Crafts alkylation with isopropyl chloride^{358, 410}) the 2-isomer predominates, and in others (e.g., iodination,^{411–413} Friedel–Crafts reaction with dialkylaminoalcohols,⁴¹⁴ and certain Friedel–Crafts alkylation reactions^{414–416}), only the 3-isomer is obtained. Friedel–Crafts alkylations, unlike the corresponding acylations, have not been extensively studied, and the results are difficult to rationalize (Section VI, C). Mononitration gives a complex mixture, the composition of which varies widely with the reaction conditions; in all cases, however, the 3-isomer predominates. Nitration occurs also in the benzene ring. Sulfonation has been little studied.

2. 2- or 3-Substituted Benzo[b]thiophenes

An electron-donating substituent in the 2- or 3-position directs substitution predominantly into the free thiophene position.

Benzo[b]thiophenes containing an electron-withdrawing group in the 3-position are sometimes resistant to bromination⁹¹; they undergo nitration⁹⁹ entirely in the benzene ring (mainly in the 4-position), and not in the 2-position as was previously⁴¹⁷ believed. Attack in the 4-position is somewhat surprising in view of the close analogy between the 3- and 4-positions in benzo[b]thiophene with the hindered *peri* positions in naphthalene.⁹⁹

The case of an electron-withdrawing group in the 2-position has been less thoroughly studied (see, e.g., Mamaev and Shkurko¹⁴¹ and Van Zyl *et al.*⁴¹²). Substitution often occurs in the benzene ring (mainly in the 4-position), but also occurs to some extent in the deactivated 3-position.

⁴¹⁰ S. F. Bedell, Ph.D. Thesis, University of Connecticut (1959); *Dissertation Abstr.* **20**, 1162 (1959).

⁴¹¹ R. T. Van Vleck, U.S. Patent 2,557,708 (1951); *Chem. Abstr.* **46**, 537 (1952).

⁴¹² G. Van Zyl, C. J. Bredeweg, R. H. Rynbrandt, and D. C. Neckers, *Can. J. Chem.* **44**, 2283 (1966).

⁴¹³ R. Gaertner, *J. Am. Chem. Soc.* **74**, 4950 (1952).

⁴¹⁴ A. C. Cope and W. D. Burrows, *J. Org. Chem.* **31**, 3093 (1966).

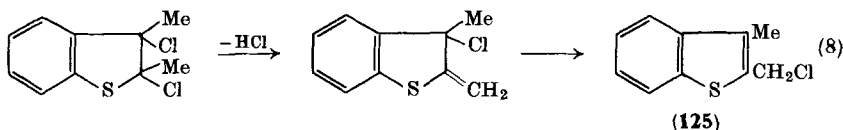
⁴¹⁵ R. E. Conary and R. F. McCleary, U.S. Patent 2,652,405 (1953); *Chem. Abstr.* **48**, 12178 (1954).

⁴¹⁶ B. B. Corson, H. E. Tiefenthal, G. R. Atwood, W. J. Heintzelman, and W. L. Reilly, *J. Org. Chem.* **21**, 584 (1956).

⁴¹⁷ N. P. Buï-Hoï and N. Hoán, *J. Chem. Soc.* 251 (1951).

3. 2,3-Disubstituted Benzo[b]thiophenes

2,3-Dibromobenzo[b]thiophene undergoes Friedel-Crafts acylation in the 6-position,⁷⁷ but gives a mixture of the 4- and 6-nitro isomer on nitration.¹⁰¹ Similarly, 2,3-dimethylbenzo[b]thiophene undergoes Friedel-Crafts acetylation^{82, 136, 418} and bromination⁸¹ mainly in



the 6-position. However, chlorination in acetic acid in the dark gives entirely the side-chain substituted compound (125).⁴¹⁹ Similarly, 2,3-dimethylbenzo[b]thiophene is nitrated in the 2-methyl group by acetyl nitrate.¹⁰⁰ One of the mechanisms proposed for side-chain chlorination involves addition of chlorine to the 2,3-double bond, followed by elimination of hydrogen chloride [Eq. (8)].⁴¹⁹ Eisch⁴²⁰ has proposed that such addition-elimination mechanisms for halogenation may be general for benzo derivatives of 5-membered heterocycles. Despite the fact that chlorination of benzo[b]thiophene itself does not apparently proceed by such a mechanism,⁴¹⁹ further examples are anticipated in the future.

4. Benzo[b]thiophenes with Substituents in the Benzene Ring

The present discussion will be confined to 5- and 6-substituted benzo[b]thiophenes, since only these have been examined systematically.

Electrophilic substitution in benzo[b]thiophenes containing a strongly electron-donating 5-substituent (e.g., OH, NH₂) is dominated by the high reactivity of the 4- and 6-(*ortho*) positions; monosubstitution occurs almost entirely in the 4-position, and disubstitution in the 4- and 6-positions.^{152, 421} The 4-position is expected to be more reactive than the 6-position because intermediate (126) retains the full resonance stabilization of the thiophene ring in contrast to intermediate 127 (for 6-substitution).⁴²² The more weakly electron-

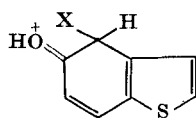
⁴¹⁸ P. Faller and P. Cagniant, *Compt. Rend.* **253**, 2997 (1961).

⁴¹⁹ E. Baciocchi and L. Mandolini, *J. Chem. Soc., B*, 397 (1968).

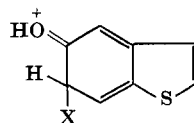
⁴²⁰ J. J. Eisch, *Advan. Heterocyclic Chem.* **7**, 1 (1966).

⁴²¹ M. Martin-Smith and M. Gates, *J. Am. Chem. Soc.* **78**, 6177 (1956).

⁴²² F. G. Bordwell and H. Stange, *J. Am. Chem. Soc.* **77**, 5939 (1955).



(126)



(127)

donating substituents, 5-NHAc, 5-OMe, still undergo monosubstitution in the 4-position, but undergo disubstitution in the 3- and 4-positions.¹⁵² Weakly activating, or deactivating, 5-substituents (e.g., acetoxy,⁴²² benzoyloxy,¹⁵² benzylsulfonyloxy,³³⁷ methane-sulfonyloxy,³³⁷ or nitro^{152, 423}) direct the attacking group into the 3-position.

6-Alkoxy-, 5,6-dimethoxy-, and 5,6-methylenedioxybenzo[b]thiophene usually undergo electrophilic substitution in the 2-position, and not in the positions *ortho* to the substituent(s), as is observed for 5-methoxy- and 5-hydroxybenzo[b]thiophene. 2-Substitution in these cases has been rationalized in terms of canonical structures involving interaction of the 6-substituent with the ring system and expansion of the sulfur valence shell.^{189, 424}

5. Benzo[b]thiophene-1,1-dioxides and Hydrobenzo[b]thiophenes

When the aromaticity of the thiophene ring in benzo[b]thiophene is destroyed, substitution is governed by the same factors which govern substitution in benzene derivatives. Thus, benzo[b]thiophene-1,1-dioxides and their 2,3-dihydro derivatives undergo substitution in the 6-position, irrespective of other substituents present in the molecule.

2,3-Dihydrobenzo[b]thiophene may be expected to behave similarly. However, although it is reported that nitration occurs in the 6-position,⁴²⁵ Friedel-Crafts acylation is said to occur in the 5-position.^{426, 427} These reactions deserve reexamination.

4,5,6,7-Tetrahydrobenzo[b]thiophene behaves as a thiophene derivative and substitution occurs, as expected, in the 2-position; or if this is already occupied, in the 3-position.

⁴²³ R. M. Scrowston and M. S. El Shanta, unpublished work (1968).

⁴²⁴ E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, **26**, 363 (1961).

⁴²⁵ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 36. Wiley (Interscience), New York, 1954.

⁴²⁶ W. Carruthers, A. G. Douglas, and J. Hill, *J. Chem. Soc.* 704 (1962).

⁴²⁷ H. C. Brown and T. Inukai, *J. Am. Chem. Soc.*, **83**, 4825 (1961).

B. HYDROBENZO[*b*]THIOPHENES

Various hydrobenzo[*b*]thiophenes have been identified in petroleum oils (Section II, A). The chemistry of hydrobenzo[*b*]thiophene-1,1-dioxides and hydrosulfurization of benzo[*b*]thiophenes are discussed in Sections VI, P, 2, *f* and VIII, respectively.

Catalytic hydrogenation of benzo[*b*]thiophene (mainly to ethylbenzene) has been studied in the presence of a molybdenum trisulfide catalyst.⁴⁰ Birch reduction of benzo[*b*]thiophene^{428, 429} and its 5-methyl derivative⁴²⁸ affords 2-ethyl- and 2-ethyl-4-methylthiophenol, respectively.

1. 2,3-Dihydrobenzo[*b*]thiophenes

2,3-Dihydrobenzo[*b*]thiophene is probably most conveniently prepared (in low yield⁴³⁰) by reduction of benzo[*b*]thiophene with sodium and alcohol.^{430, 431} It can also be prepared, as can its alkyl derivatives, by modified Wolff-Kishner^{281, 426} or Clemmensen¹⁸² reduction of the corresponding thioindoxyl. 3-Methylbenzo[*b*]thiophene is reduced catalytically to its 2,3-dihydro derivative,²⁷⁵ and 2-ethyl-2,3-dihydrobenzo[*b*]thiophene is the product of decarboxylation of the corresponding 7-carboxylic acid.²⁸¹ Sodium amalgam reduction of benzo[*b*]thiophene-2(or 3)-carboxylic acid affords the corresponding dihydro compound.²¹² Reduction of the corresponding 2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide with lithium aluminum hydride is undoubtedly the best procedure for the preparation of 2,3-dihydrobenzo[*b*]thiophenes (see Section VI, P, 2, *f*).

Reduction of thioindoxyl and its 2-ethyl derivative with sodium borohydride, followed by alkaline decomposition of the reaction mixture, affords the corresponding 2,3-dihydrobenzo[*b*]thiophene-3-ol.^{222, 432}

2-Arylidene-2,3-dihydrobenzo[*b*]thiophen-3-ones (**128**) may also be reduced with sodium borohydride [Eq. (9)].²²² Treatment with an excess of sodium borohydride gives the 2-benzyl-3-hydroxy-2,3-

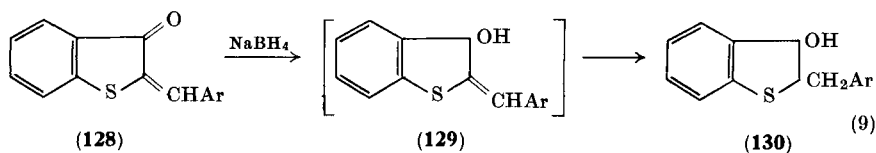
⁴²⁸ M. Nakazaki, *Nippon Kagaku Zasshi* **80**, 687 (1959); *Chem. Abstr.* **55**, 3553 (1961).

⁴²⁹ W. Hüchel and I. Nabih, *Chem. Ber.* **89**, 2115 (1956).

⁴³⁰ S. F. Birch, *J. Inst. Petrol.* **40**, 76 (1954).

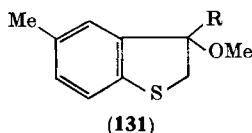
⁴³¹ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), pp. 34-45. Wiley (Interscience), New York, 1954.

⁴³² N. Kucharczyk and V. Horák, *Chem. & Ind. (London)* 976 (1964).



dihydrobenzo[*b*]thiophenes (130); the intermediates (129) can sometimes be obtained under carefully controlled conditions. The alcohols (130) readily lose water on treatment with acid to give the corresponding 2-arylbenzo[*b*]thiophenes.²²² Several 2-arylidene-2,3-dihydrobenzo[*b*]thiophen-3-ones have been reduced by lithium aluminum hydride⁴³³; acidification of the reaction mixture affords the corresponding 2-arylbenzo[*b*]thiophene.

The preparation of 2,3-dihydrobenzo[*b*]thiophene by the action of sodium hydroxide on certain sulfonium salts⁴²⁵ has been improved by Guerra³⁴⁷ and extended to the preparation of several 5-methylbenzo[*b*]thiophenes (Section IV, F) through the intermediates (131); these readily lose methanol on treatment with hydrogen bromide in acetic acid.



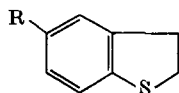
Treatment of 3-cyanobenzo[*b*]thiophene with *tert*-butylmagnesium chloride, followed by the addition of acid to the reaction mixture, does not give the ketone; instead a Michael-type addition occurs to give 2-*tert*-butyl-3-cyano-2,3-dihydrobenzo[*b*]thiophene.⁴³⁴

2,3-Dihydrobenzo[*b*]thiophene⁴²⁶ and its 2-methyl derivative¹⁸² are readily dehydrogenated with sulfur to the corresponding benzo[*b*]thiophene. 2,3-Dihydrobenzo[*b*]thiophenes are oxidized by peracetic acid to the corresponding sulfones (Section VI, P, 2), and give crystalline complexes with mercuric chloride.

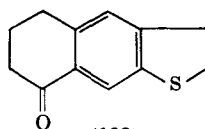
Friedel-Crafts acylation of 2,3-dihydrobenzo[*b*]thiophene using succinic anhydride⁴²⁶ or acetyl chloride⁴²⁷ affords the 5-substituted

⁴³³ O. P. Shkurko, *Izv. Sibirsk. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* 135 (1965); *Chem. Abstr.* 63, 11474 (1965).

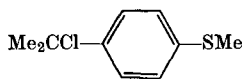
⁴³⁴ M. Martynoff, *Compt. Rend.* 242, 1039 (1956).



(132a) R = COMe

(132b) R = CO(CH₂)₂CO₂H(132c) R = (CH₂)₃CO₂H(132d) R = C(OH)Me₂(132e) R = CClMe₂

(133)



(134)

derivatives (132b and 132a, respectively). Using the Huang–Minlon procedure, the acid (132b) can be reduced to 132c, which cyclizes to give the naphtho[2,3-*b*]thiophene derivative (133) on treatment with hydrofluoric acid. In contrast to Friedel–Crafts acylation, nitration of 2,3-dihydrobenzo[*b*]thiophene is said to give the 6-nitro derivative.⁴²⁵

Compound 132a affords the carbinol (132d) on treatment with methylmagnesium iodide; treatment of 132d with hydrogen chloride in methylene chloride affords the unstable chloro compound (132e).⁴²⁷ A study of the rates of solvolysis of 132e and *p*-methylthio-*tert*-cumylchloride (134) under identical conditions leads to the conclusion that there is no significant inhibition of resonance in 134, which might have occurred if the methyl group had forced the SMe group out of the plane of the benzene ring.

The equilibrium constant for the dissociation of the cyanohydrin of 5-acetyl-2,3-dihydrobenzo[*b*]thiophene has been determined.⁴³⁵

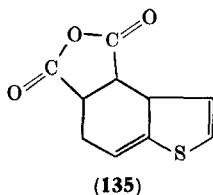
2. 4,5- and 6,7-Dihydrobenzo[*b*]thiophenes

The parent compounds are unknown, but several derivatives have been prepared (Sections VI, B, 4 and VI, I, 4).

3. 3a,4,5,6-Tetrahydrobenzo[*b*]thiophenes

2-Vinylthiophene and maleic anhydride afford a Diels–Alder adduct which is believed to have the structure 135.^{366, 367} Hydrolysis of 135 and subsequent dehydrogenation of the product with sulfur gives benzo[*b*]thiophene-4,5-dicarboxylic anhydride,³⁶⁷ whereas dehydrogenation of 135 with sulfur, followed by hydrolysis and decarboxylation, affords benzo[*b*]thiophene.³⁶⁶

⁴³⁵ M. J. Y. Foley, N. H. P. Smith, and P. Watts, *Tetrahedron* **20**, 1555 (1964).



4. 4,5,6,7-Tetrahydrobenzo[*b*]thiophenes

A number of 4,5,6,7-tetrahydrobenzo[*b*]thiophenes have been synthesized recently from cyclohexanones (Section IV, A). Hydrolysis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate, prepared in this way, affords the free amino acid, which readily loses carbon dioxide to yield 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene in 71% overall yield.²⁵⁴

4,5,6,7-Tetrahydrobenzo[*b*]thiophene may be prepared by Clemmensen³⁵⁵ or Huang-Minlon^{194, 356, 436} reduction of 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one (**103**) or by Wolff-Kishner reduction of 4,5,6,7-tetrahydrobenzo[*b*]thiophen-7-one (**104**).³⁶³ Its 2-¹⁹⁴ and 5-ethyl,⁴³⁷ 5- and 6-methyl,³⁵⁷ and 2-isopropyl³⁵⁸ derivatives may be prepared similarly. 2-Methyl-,⁴³⁶ 5-methyl-,⁴³⁷ 5-ethyl-,⁴³⁷ and 2,3-diethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene¹⁹⁴ may be obtained by Clemmensen or Wolff-Kishner reduction of the appropriate formyl or acetyl derivative. 4,5,6,7-Tetrahydrobenzo[*b*]thiophene-2-carboxaldehyde¹⁹³ may be prepared by treating a corresponding Grignard reagent with ethyl orthoformate.

The synthesis of 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one and -7-one has been described in Section IV, G; 4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-one is obtained on oxidation of **136** (R = Me) with perbenzoic acid.⁴³⁸

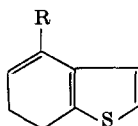
4,5,6,7-Tetrahydrobenzo[*b*]thiophene behaves like thiophene in electrophilic substitution reactions. Thus, it is formylated with a mixture of *N*-methylformanilide and phosphorus oxychloride,⁴³⁶ iodinated in the presence of mercuric oxide,¹⁹³ and brominated by *N*-bromosuccinimide,¹⁹³ all in the 2-position; in Friedel-Crafts reactions with acetyl chloride,^{194, 436} propionyl chloride,⁴³⁶ succinic

⁴³⁶ N. P. Buü-Hoï and M. Khenissi, *Bull. Soc. Chim. France* 359 (1958).

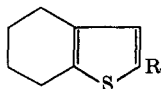
⁴³⁷ M. Maillet and M. Sy, *Compt. Rend.* **C266**, 1545 (1968).

⁴³⁸ D. A. H. Taylor, *W. African J. Biol. Appl. Chem.* **7**, 14 (1963).

anhydride,⁴³⁹ glutaric anhydride,⁴⁴⁰ or the ester chloride of glutaric acid⁴⁴⁰ it also affords the 2-substituted derivatives (**137a-e**). Attempted chloromethylation gives only resins.¹⁹³ If the 2-position is substituted, reaction occurs in the 3-position; e.g., Friedel-Crafts acylation of 2-methyl-⁴³⁶ or 2-ethyl-4,5,6,7-tetrahydrobenzo[*b*]-thiophene¹⁹⁴ and iodination of the 2-methyl derivative in the presence of mercuric oxide.¹⁹³



(136)

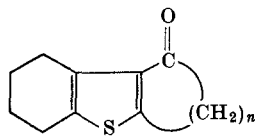


(137a) R = COMe

(137b) R = COEt

(137c) R = CO(CH₂)₂CO₂H(137d) R = CO(CH₂)₃CO₂H(137e) R = CO(CH₂)₃CO₂Et

(137f) R = Et

(137g) R = Prⁿ(137h) R = (CH₂)₃CO₂H(137i) R = (CH₂)₄CO₂H(137j) R = (CH₂)₄CO₂Et

(138a) n = 3

(138b) n = 4

Huang-Minlon reduction of compounds **137a-e** affords compounds **137f-j**^{194, 436, 439, 440} and Friedel-Crafts cyclization of the acid chlorides of **137h** and **137i** affords **138a**⁴³⁹ and **138b**,⁴⁴⁰ respectively. Oxidation of either **137a**¹⁹⁴ or **137d**⁴⁴⁰ with hypobromite, or of 4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxaldehyde,⁴³⁶ gives 4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylic acid.

4,5,6,7-Tetrahydrobenzo[*b*]thiophene-2-carboxaldehyde condenses with compounds containing a CH₂CN group.⁴³⁶ 2-Acetyl- and 2-propionyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene undergo the Pfitzinger reaction with isatins.⁴³⁶ Attempts to prepare 2-cyano-4,5,6,7-tetra-

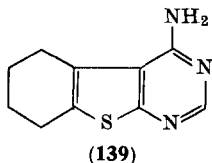
⁴³⁹ P. Cagniant and P. Cagniant, *Bull. Soc. Chim. France* 336 (1952).

⁴⁴⁰ P. Cagniant and P. Cagniant, *Bull. Soc. Chim. France* 921 (1953).

hydrobenzo[b]thiophene by treating the 2-bromo derivative with cuprous cyanide, and 2-bromomethyl-4,5,6,7-tetrahydrobenzo[b]thiophene by treating the 2-methyl derivative with *N*-bromosuccinimide, were unsuccessful.¹⁹³

Ethyl 2-acetamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate,⁴⁴¹ 2-acetamido-3-benzoyl(or -3-cyano)-,¹¹⁴ 5-methyl-,⁴³⁷ and 5-ethyl-4,5,6,7-tetrahydrobenzo[b]thiophene⁴³⁷ may be aromatized by heating them with sulfur or selenium.

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate affords a glycine derivative when treated with ethyl chloroacetate in



methylformamide⁴⁴² or dimethylformamide.⁴⁴³ Successive treatment of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene with ethyl orthoformate and ammonia yields a formamidine derivative which, on being heated in dimethylformamide with a trace of sodium methoxide, affords the pyrimidine derivative (139).⁴⁴⁴

Bromination (Br_2) of 4,5,6,7-tetrahydrobenzo[b]thiophen-4-one affords either a 2-bromo or a 5-bromo derivative, depending on whether the reaction is carried out at 0° in ether,^{445, 446} or at -5 to 0° in 50% aqueous acetic acid.³⁵⁴ The 5-bromo derivative condenses with morpholine or potassium phthalimide to give **140a** or **140b**, respectively.^{445, 446} Hydrazinolysis of **140b** fails to give any of the 5-amino derivative.^{445, 446} On nitration, the 2-bromo derivative affords the 3-nitro compound or **141** ($\text{R}=\text{NO}_2$), depending on the reaction conditions.³⁵⁴ With sodium azide in PPA the 2-bromo and 2-bromo-3-

⁴⁴¹ K. Gewald, G. Neumann, and H. Böttcher, *Z. Chem.* **6**, 261 (1966).

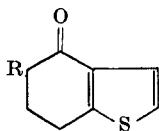
⁴⁴² V. I. Shvedov and A. N. Grinev, *Zh. Organ. Khim.* **1**, 2228 (1965); *Chem. Abstr.* **64**, 11149 (1966).

⁴⁴³ V. I. Shvedov and A. N. Grinev, U.S.S.R. Patent 170,530 (1965); *Chem. Abstr.* **63**, 13411 (1965).

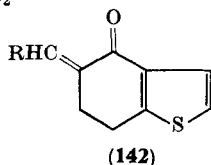
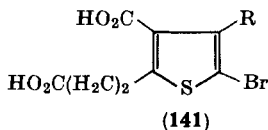
⁴⁴⁴ E. C. Taylor and J. G. Berger, *Angew. Chem.* **78**, 144 (1966); *Angew. Chem. Intern. Ed. Engl.* **5**, 131 (1966).

⁴⁴⁵ J. Sam and G. G. Advani, *J. Pharm. Sci.* **54**, 753 (1965).

⁴⁴⁶ J. Sam, U.S. Patent 3,316,258 (1967).

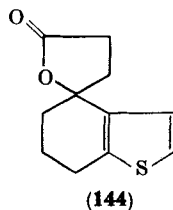
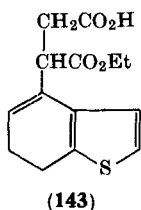


- (140a) R = piperidino
 (140b) R = phthalimido
 (140c) R = COMe
 (140d) R = COCO₂Et
 (140e) R = Et
 (140f) R = CO₂Et
 (140g) R = CH₂NR₂



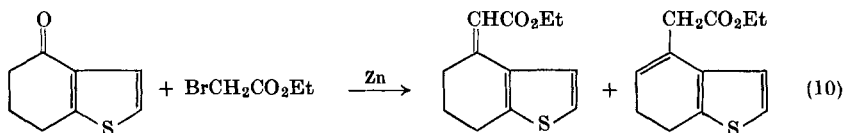
nitro derivatives afford **141** (R = H) and **141** (R = NO₂), respectively.³⁵⁴

4,5,6,7-Tetrahydrobenzo[*b*]thiophen-4-one undergoes condensation with ethyl formate,⁴³⁷ ethyl acetate,⁴³⁷ or ethyl oxalate³⁵⁶ to give **142** (R = OH), 5-acetyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one (**140c**), and **140d**, respectively. The hydroxymethylene compound (**142**; R = OH) affords the olefin (**142**; R = Me) on successive treatment with methylmagnesium iodide and acid; on successive ethylation and hydrolysis, it yields 5-ethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one (**140e**).⁴³⁷ Compound **140d** loses carbon monoxide on being heated to give **140f**.³⁵⁶



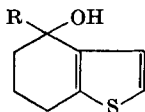
4,5,6,7-Tetrahydrobenzo[*b*]thiophen-4-one undergoes the Stobbe condensation with diethyl succinate to give the half-ester (**143**), hydrolysis of which yields the corresponding diacid.⁴⁴⁷ Decarboxylation of the diacid affords the spiro lactone (**144**).

⁴⁴⁷ D. G. Hawthorne and Q. N. Porter, *Australian J. Chem.* **19**, 1909 (1966).



In a Reformatsky reaction with ethyl bromoacetate, 4,5,6,7-tetrahydrobenzo[b]thiophen-4-one affords a mixture of two esters [Eq. (10)].^{355, 448} 4,5,6,7-Tetrahydrobenzo[b]thiophen-7-one behaves analogously.³⁶³

4,5,6,7-Tetrahydrobenzo[b]thiophen-4-one undergoes the Mannich reaction with various amines to give Mannich bases (**140g**).^{219, 445, 449} Some of these have been shown to react with Grignard reagents to give carbinols (**24**), which readily lose water on treatment with acid to give derivatives of 6,7-dihydrobenzo[b]thiophene.²¹⁹ 4,5,6,7-Tetrahydrobenzo[b]thiophen-4-one reacts similarly with methyl-^{355, 450}



(145a) R = Me

(145b) R = Ph

(145c) R = *o*-MeC₆H₄

(145d) R = *m*-MeC₆H₄

(145e) R = *p*-MeC₆H₄

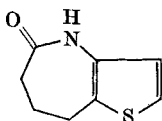
and arylmagnesium bromides^{355, 356} to give alcohols (**145**). These readily lose water on treatment with acid to give the corresponding 6,7-dihydrobenzo[b]thiophene derivatives (**136**; R = Me or Ar), which afford 4-methyl-³⁵⁵ and 4-arylbenzo[b]thiophenes,^{355, 356} respectively, on aromatization with sulfur. In addition to 4-phenyl-6,7-dihydrobenzo[b]thiophene, acid-catalyzed dehydration of **145b** also affords 4-phenylbenzo[b]thiophene, 4-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene, 3-benzylthiophene, and a product which is thought to be 4-phenyl-2,3-dihydrobenzo[b]thiophene.³⁵⁶ Dehydration of **145c, d-e** is said to afford similar mixtures of products. The mechanism of these rearrangements has not been discussed.

⁴⁴⁸ M. C. Kloetzel and D. M. Frisch, U.S. Patent 2,930,800 (1960); *Chem. Abstr.* **54**, 16465 (1960).

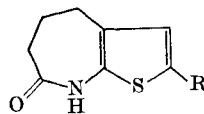
⁴⁴⁹ J. Sam, U.S. Patent 3,316,259 (1967); *Chem. Abstr.* **68**, 12855 (1968).

⁴⁵⁰ D. A. H. Taylor, *J. Chem. Soc.* 2767 (1959).

2-*tert*-Butyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one undergoes a Pfitzinger reaction with isatin.³⁵⁹ The 3-*tert*-butyl isomer, however, is virtually unreactive under similar conditions owing to steric hindrance by the bulky *tert*-butyl group.



(146)



(147)

The oximes of 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one and -7-one undergo the Beckmann rearrangement to give **146**^{354, 451} and **147** (R = H),³⁶² respectively. Compound **147** (R = Cl) may be prepared similarly and by treating 2-chloro-4,5,6,7-tetrahydrobenzo[*b*]thiophen-7-one with ammonia in the presence of PPA.³⁵⁶ The oxime of 4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-one affords 4-aminobenzo[*b*]thiophene in a modified Leuckart reaction.^{241, 355} The same oxime may be converted into 4-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene by reduction with aluminum amalgam in methanol.⁴⁵² The parent ketone also affords 4-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene on reaction with formamide at 165°, followed by acidic hydrolysis of the resulting 4-formylamino compound.³⁵⁵

4,5,6,7-Tetrahydrobenzo[*b*]thiophen-4-one may be converted into 4-hydroxybenzo[*b*]thiophene by heating it with sulfur,⁴⁵³ or by catalytic dehydrogenation.^{454, 455} 5-Methyl- and 5-ethyl-4-hydroxybenzo[*b*]thiophene may be prepared similarly.⁴³⁷

5. 2,4,5,6,7,7a-Hexahydrobenzo[*b*]thiophen-4-one (49b)

This compound has been synthesized recently by treating 3-mercaptocyclohexanone with chloroacetaldehyde in the presence of

⁴⁵¹ B. P. Fabrichnyi, I. F. Shalavina, and Y. L. Gol'dfarb, *Zh. Obshch. Khim.* **31**, 1244 (1961); *Chem. Abstr.* **55**, 23488 (1961).

⁴⁵² Ya. L. Gol'dfarb, E. A. Krasnyanskaya, and B. P. Fabrichnyi, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 1825 (1962); *Chem. Abstr.* **58**, 8922 (1963).

⁴⁵³ H. A. Kaufman, J. R. Kilsheimer, and H. M. Foster, U.S. Patent 3,317,552 (1967); *Chem. Abstr.* **68**, 39463 (1968).

⁴⁵⁴ Mobil Oil Corp., Netherlands Patent Appl. 6,604,433 (1966); *Chem. Abstr.* **67**, 32584 (1967).

⁴⁵⁵ H. A. Kaufman and J. R. Kilsheimer, U.S. Patent 3,335,152 (1967); *Chem. Abstr.* **68**, 104969 (1968).

catalytic quantities of acid²⁵⁸ and by acidic hydrolysis of the condensation product formed between 3-mercaptopcyclohexanone ethylene ketal and chloroacetaldehyde (Section IV, A).²⁵⁹

6. *Cis- and Trans-Octahydrobenzo[b]thiophene*

Reduction of *cis*-octahydrobenzo[b]thiophene-1,1-dioxide (Section VI, P, 2, *f*) with lithium aluminum hydride gives *cis*-octahydrobenzo[b]thiophene (48).²⁷ The *trans* isomer is obtained similarly from the *trans*-1,1-dioxide, formed by isomerization of the *cis*-1,1-dioxide.²⁷ *cis*-Octahydrobenzo[b]thiophene may also be prepared from the cyclohexene derivative (47) (Section IV, A).

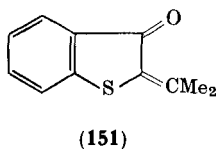
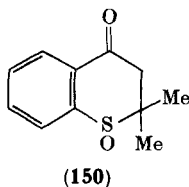
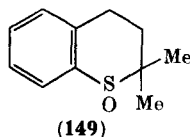
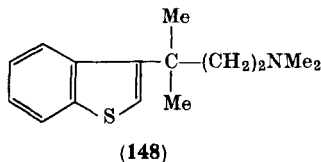
C. DERIVATIVES WITH A HYDROCARBON SIDE CHAIN

1. *Alkylbenzo[b]thiophenes*

Alkylbenzo[b]thiophenes are usually prepared by ring closure (Section IV). They may also be prepared by dehydrogenation of hydrobenzo[b]thiophenes (Section VI, B) and by Clemmensen or Wolff-Kishner reduction of acylbenzo[b]thiophenes (Section VI, L). 2-Methyl- and 2-ethylbenzo[b]thiophene are most conveniently prepared by treatment of 2-benzo[b]thienyllithium with the appropriate dialkyl sulfate (Section VII). Mono- and dimethyl-2,3-dihydrobenzo[b]thiophene-1-oxides (Section VI, P, 1) are dehydrated by acetic anhydride to give the corresponding benzo[b]thiophenes.²⁸⁰

Friedel-Crafts alkylation of benzo[b]thiophene has received little attention. The published results, which deserve reexamination, indicate that exclusive 3-substitution occurs in some cases, whereas in others, 2-substitution predominates. Benzo[b]thiophene is alkylated with isopropyl chloride, isopropanol, or propene in the presence of various acid catalysts under a variety of reaction conditions to give a mixture of 2- and 3-isopropylbenzo[b]thiophene in which the 2-isomer predominates (78–92%).^{358, 410} In contrast, alkylation with isobutene in the presence of either 80% sulfuric acid⁴¹⁵ or 100% phosphoric acid⁴¹⁶ is said to afford exclusively 3-*tert*-butylbenzo[b]thiophene in yields of 100 and 75%, respectively. In neither case was the structure of the product rigorously confirmed. Likewise, 3-*tert*-amylbenzo[b]thiophene is the exclusive product of alkylation with *tert*-amyl alcohol in the presence of stannic chloride⁴¹⁴; alkylation with pent-1-ene, hex-1-ene, and a C₁₈ propylene polymer is also claimed to give 3-monoalkylated benzo[b]thiophenes.⁴¹⁵ Nonselectivity in Friedel-

Crafts alkylation is, of course, well known in the benzene series,⁴⁵⁶ and has also been observed with thiophene. The proportion of 2- to 3-isomer in the case of thiophene varies from 1:1 to 3:1, depending on the reagent and catalyst used.³ The 3-*tert*-amylbenzo[*b*]thiophene



obtained by Friedel-Crafts alkylation has been shown to be identical with a sample prepared by Hofmann exhaustive methylation of the amine (148), followed by reduction of the product (Section VI, H),⁴¹⁴ and 2- and 3-isopropylbenzo[*b*]thiophene, obtained similarly, have been identified with samples prepared from the corresponding isopropenyl derivatives.^{358,410} 2-Isopropylbenzo[*b*]thiophene is the major product of the photochemical rearrangement of 2,2-dimethylthiachroman-1-oxide (149).⁴⁵⁷ The mechanisms of this and the related thermal rearrangement of 150 to 151 in acetic anhydride⁴⁵⁸ have been discussed.⁴⁵⁷

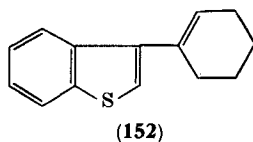
2. Arylbenzo[*b*]thiophenes

Arylbenzo[*b*]thiophenes can be prepared by ring closure (Section IV); 2-phenylbenzo[*b*]thiophene may be prepared by treating 2-benzo[*b*]thienyllithium with fluorobenzene^{185,307} and 4- and 7-phenylbenzo[*b*]thiophene can be synthesized from 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one and -7-one, respectively (Section VI, B, 4). Arylbenzo[*b*]thiophenes have been synthesized by cyclodehydration of keto-derivatives (Section VI, L, 3). 6-Phenylbenzo[*b*]thiophene has not yet been reported.

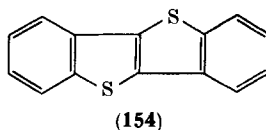
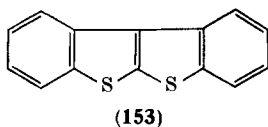
⁴⁵⁶ A. W. Francis, *Chem. Rev.* **43**, 257 (1948).

⁴⁵⁷ R. A. Archer and B. S. Kitchell, *J. Am. Chem. Soc.* **88**, 3462 (1966).

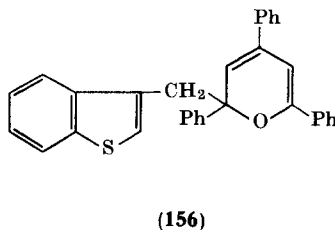
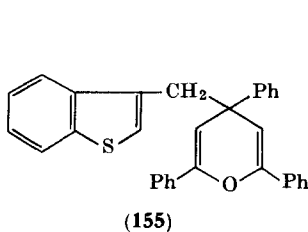
⁴⁵⁸ R. B. Morin, 148th Natl. Meeting Am. Chem. Soc., Chicago (1964); see Archer and Kitchell.⁴⁵⁷



3-Phenylbenzo[b]thiophene may be prepared by dehydrogenation of the olefin (152) with chloranil¹⁸⁶; use of sulfur gives the 2-phenyl isomer.^{185, 349} 3-(1-Naphthyl)-,^{308, 309, 349} and 3-(2-naphthyl)benzo[b]thiophene³⁰⁹ may be prepared by analogous methods. 3-Phenylbenzo[b]thiophene is also obtained by decarboxylation of the corresponding 2-carboxylic acid¹⁸⁵ and by reaction of thioindoxyl with phenylmagnesium bromide.³⁰⁹ The latter method may be extended to the preparation of 3-(2-thienyl)benzo[b]thiophene.³⁰⁹ 2-(2-Naphthyl)benzo[b]thiophene is obtained when crude naphthalene is purified by heating it with fuller's earth.⁵⁴ The rearrangements of 3-phenylbenzo[b]thiophene and its derivatives to their 2-isomers are discussed in



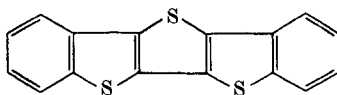
Section IV, C. 3-Phenylbenzo[b]thiophene is converted into **153** by heating it with sulfur; the same reaction in the presence of aluminum chloride gives **154**, probably owing to an initial rearrangement of the starting material to the 2-isomer.^{293, 308, 459}



⁴⁵⁹ T. S. Murthy, L. J. Pandya, and B. D. Tilak, *J. Sci. Ind. Res. (India)* **20B**, 169 (1961).

Treatment of 2,4,6-triphenylpyrylium perchlorate with 3-benzo[*b*]-thienylmethylmagnesium bromide affords the 4*H*-pyran (**155**),⁴⁶⁰ which undergoes allylic rearrangement in diethylene glycol in the presence of sodium to give the 2*H*-pyran (**156**).⁴⁶¹ Under the same reaction conditions **156** is further converted by an intramolecular aldol condensation into 3-(2,4,6-triphenylphenyl)benzo[*b*]thiophene.

In 1952, the only known dibenzo[*b*]thienyls were the 2,2'- and 2,3'-isomers.⁴⁶² Since then, 2,3'-, 3,3'-, and 5,5'-dibenzo[*b*]thienyl have been prepared by ring closure (Section IV, C), while 2,2'- and 3,3'-dibenzo[*b*]thienyls in general are formed by treating a 2-benzo[*b*]thienyllithium compound (Section VII) or a benzo[*b*]thienylmagnesium halide (Section VI, D, 2) with cupric chloride. It should be noted that treatment of 3-benzo[*b*]thienylmagnesium iodide with cupric chloride affords not only the expected 3,3'-dibenzo[*b*]thienyl, but also the 2,3'- and 2,2'-isomers by rearrangement.³⁰⁵ The Ullmann reaction on 3-iodobenzo[*b*]thiophene probably does not give 3,3'-dibenzo[*b*]thienyl,³⁰⁵ as was previously thought.³⁴⁹ The reaction of 2,2'-, 2,3'-, and 3,3'-dibenzo[*b*]thienyl with sulfur in the presence or absence, of aluminum chloride may give rise to complex mixtures.^{228, 308, 459, 463}



(157)

For example, when the 2,2'-isomer is treated with sulfur in the presence of aluminum chloride, it affords **157**; with aluminum chloride alone it affords its 2,3'-isomer as one of a mixture of products.^{223, 308, 463}

3. *Aralkylbenzo[*b*]thiophenes*

Aralkylbenzo[*b*]thiophenes may be prepared by Clemmensen or Wolff-Kishner reduction of aroylbenzo[*b*]thiophenes (Section VI, L, 3),

⁴⁶⁰ K. Dimroth, K. Wolf, and H. Kroke, *Ann. Chem.* **678**, 183 (1964).

⁴⁶¹ K. Dimroth, H. Kroke, and K. Wolf, *Ann. Chem.* **678**, 202 (1964).

⁴⁶² H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 27. Wiley (Interscience), New York, 1954.

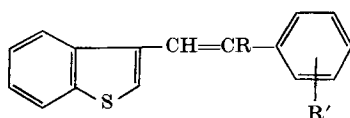
⁴⁶³ L. J. Pandya, G. N. Pillai, and B. D. Tilak, *J. Sci. Ind. Res. (India)* **18B**, 198 (1959).

by reduction of 2-arylidene-2,3-dihydrobenzo[*b*]thiophen-3-ones with sodium borohydride or lithium aluminum hydride (Section VI, B, 1), by the action of carbon dioxide on benzo[*b*]thienylmethylmagnesium halides or of phenyllithium on the corresponding bromomethylbenzo[*b*]thiophenes (in these cases coupling occurs to give 1,2-dibenzo[*b*]thienylethanes) (Section VI, D, 4), and by condensation of benzo[*b*]thiophene with formaldehyde (Section VI, J).

2-Benzylbenzo[*b*]thiophene¹³² and 2-*p*-methoxybenzylbenzo[*b*]thiophene and its 3-ethyl derivative⁴⁶⁴ may be prepared by treating 2-benzo[*b*]thienyllithium or its 3-ethyl derivative with benzyl chloride or anisyl chloride, respectively. Various *p*-methoxybenzylbenzo[*b*]thiophenes may be prepared by Friedel-Crafts reactions between the appropriate benzo[*b*]thiophene and anisyl chloride.⁴⁶⁴

4. Alkenylbenzo[*b*]thiophenes

The preparation of various alkenylbenzo[*b*]thiophenes by dehydration of side-chain alcohols is discussed in Section VI, J. 1,1-Di(2-benzo[*b*]thienyl)ethylene may be prepared by treating 2-benzo[*b*]thienyllithium with acetyl chloride,¹³² and the olefins (158a-d) may



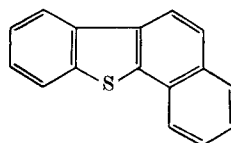
(158a) R = Me, R' = H

(158b) R = H, R' = *o*-Me

(158c) R = H, R' = *m*-Me

(158d) R = H, R' = *p*-Me

(158e) R = R' = H



(159)

be conveniently prepared by treating 3-benzo[*b*]thienylmethylphosphonium chloride with *n*-butyllithium, followed by the addition of acetophenone or *o*-, *m*-, or *p*-tolualdehyde, respectively (Wittig reaction).⁴⁶⁵

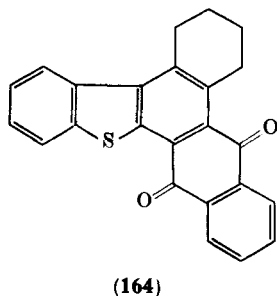
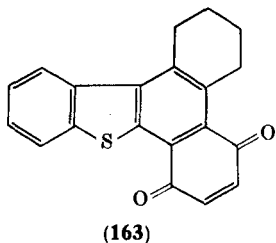
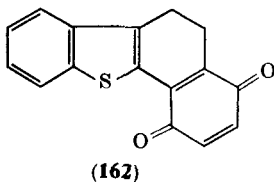
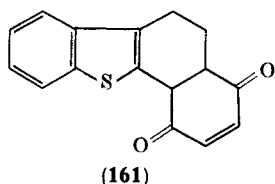
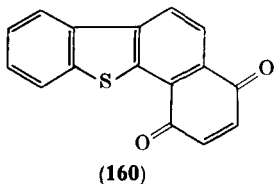
Photoirradiation of 158e in the presence of iodine affords the benzo[*b*]naphtho[2,1-*d*]thiophene (159); 158a-d similarly give the appropriate methyl-substituted compounds.⁴⁶⁵ With ethyl diazo-

⁴⁶⁴ R. Royer, P. Demerseman, J.-P. Lechartier, and A. Cheutin, *J. Org. Chem.* **27**, 3808 (1962).

⁴⁶⁵ W. Carruthers and H. N. M. Stewart, *J. Chem. Soc.* 6221 (1965).

acetate, 2-vinylbenzo[*b*]thiophene affords a mixture of *cis*- and *trans*-ethyl 2-(2-benzo[*b*]thienyl)cyclopropanecarboxylate.⁴⁶⁶ The corresponding reaction with 3-vinylbenzo[*b*]thiophene gives only the *trans* ester. When 3-vinylbenzo[*b*]thiophene is heated with sulfur, it affords a mixture of products from which none of the expected thieno[2,3-*b*]benzo[*b*]thiophene can be isolated.⁴⁶⁷

3-Vinylbenzo[*b*]thiophene undergoes Diels-Alder reactions with benzyne,⁴⁶⁸ maleic anhydride,⁴⁶⁹ benzo[*b*]thiophene-1,1-dioxide,⁴⁶⁹ *p*-benzoquinone, and various 1,4-naphthaquinones.^{469, 470} With quinones, the product depends on the reaction conditions. For



⁴⁶⁶ C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngibl, *J. Med. Pharm. Chem.* **5**, 1243 (1962); C. Kaiser and C. L. Zirkle, U.S. Patent 3,010,971 (1960); *Chem. Abstr.* **56**, 15484 (1962).

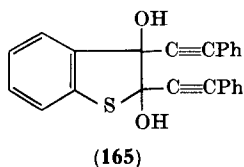
⁴⁶⁷ W. E. Parham and B. Gadsby, *J. Org. Chem.* **25**, 234 (1960).

⁴⁶⁸ T. G. Corbett and Q. N. Porter, *Australian J. Chem.* **18**, 1781 (1965).

⁴⁶⁹ W. Davies and Q. N. Porter, *J. Chem. Soc.* 4961 (1957).

⁴⁷⁰ W. Davies, Q. N. Porter, and J. R. Wilmshurst, *J. Chem. Soc.* 3366 (1957).

example, with an excess of *p*-benzoquinone, the fully aromatized product (**160**) is obtained; with an excess of the vinyl compound and a short reaction time, the product is **161** and, by using a dilute solution of the reactants and a short reaction time, a compound can be isolated for which structure **162** has been proposed.^{469, 470} 2-Vinylbenzo[*b*]thiophene affords an adduct with 1,4-naphthaquinone⁴⁷¹; other Diels–Alder reactions have not been investigated. 1-(3-Benzo[*b*]thienyl)cyclohexene (**152**) reacts with *p*-benzoquinone or 1,4-naphthaquinone to give only **163** or **164**, respectively.⁴⁶⁹



2,3-Di(phenylethynyl)-2,3-dihydrobenzo[*b*]thiophene-2,3-diol (**165**) is obtained on treating benzo[*b*]thiophene-2,3-quinone with lithium phenylacetylide. It is converted into 2,3-di(phenylethynyl)benzo[*b*]thiophene on treatment with stannous chloride.⁴⁷²

D. HALOGEN DERIVATIVES

1. Preparation of Halobenzo[*b*]thiophenes

a. *By Direct Halogenation.* Controlled chlorination^{419, 473–475} of benzo[*b*]thiophene at room temperature gives mainly 3-chlorobenzo[*b*]thiophene (69%), together with some 2,3-dichloro- (28%), and a small amount of 2-chlorobenzo[*b*]thiophene (3%).⁴¹² Bromination gives similar results,^{107, 412, 476–478} but a higher yield (92%) of 3-

⁴⁷¹ W. H. Cherry, W. Davies, B. C. Ennis, and Q. N. Porter, *Australian J. Chem.* **20**, 313 (1967).

⁴⁷² W. Ried and E. Suarez-Rivero, *Chem. Ber.* **96**, 1475 (1963).

⁴⁷³ A. H. Schlesinger and D. T. Mowry, *J. Am. Chem. Soc.* **73**, 2614 (1951).

⁴⁷⁴ R. F. McCleary and J. A. Patterson, U.S. Patent 2,571,742 (1951); *Chem. Abstr.* **46**, 8152 (1952).

⁴⁷⁵ W. Davies, F. C. James, S. Middleton, and Q. N. Porter, *J. Chem. Soc.* 1565 (1955).

⁴⁷⁶ G. M. Badger, P. Cheuchit, and W. H. F. Sasse, *Australian J. Chem.* **17**, 371 (1964).

⁴⁷⁷ W. Ried and H. Bender, *Chem. Ber.* **88**, 34 (1955).

⁴⁷⁸ P. Faller, *Bull. Soc. Chim. France* 3618 (1966).

bromobenzo[*b*]thiophene can be obtained by using carefully controlled conditions.⁴⁷¹ An excess of chlorine or bromine gives the 2,3-dihalo compound in high yield.^{107, 473, 477} The claim⁴⁷⁹ that chlorination of benzo[*b*]thiophene gives the 2,5-dichloro compound is probably a misprint, since the physical characteristics of the product are identical with those of 2,3-dichlorobenzo[*b*]thiophene. The kinetics of the chlorination of benzo[*b*]thiophene at low temperatures have been studied,⁴¹⁹ and a general comparative account of the mechanisms of halogenation of benzofuran, benzo[*b*]thiophene, and indole has been given.⁴²⁰

Iodination of benzo[*b*]thiophene in benzene in the presence of mercuric oxide gives exclusively 3-iodobenzo[*b*]thiophene.⁴¹¹⁻⁴¹³

Fluorination of benzo[*b*]thiophene in the vapor phase with cobalt trifluoride gives mainly perfluoroethylcyclohexane, formed by fission of the molecule, elimination of sulfur, and fluorination of the hydrocarbon fragment.⁴⁸⁰

Bromination of 2-methyl-,^{447, 481} 7-methyl-,^{78, 478} 5-bromo-,⁷⁶ 2-fluoro-,⁴⁸² or 2-phenylbenzo[*b*]thiophene⁴⁸³ in either chloroform or carbon tetrachloride gives the 3-bromo compound in each case. 2-(2-Naphthyl)benzo[*b*]thiophene is brominated,⁵⁴ chlorinated, and iodinated⁴⁸⁴ in the 3-position. In the cases of 3-methyl-⁴⁸⁵ and 3-bromobenzo[*b*]thiophene,¹⁰⁷ bromination takes place in the 2-position. Bromination of 2,3-dimethylbenzo[*b*]thiophene in dilute chloroform solution at 0° gives mainly nuclear substitution in the 6-position,⁸¹ but chlorination in acetic acid causes substitution in the 2-methyl group, to give 2-chloromethyl-3-methylbenzo[*b*]thiophene.⁴¹⁹

Bromination of 2,3,5-trimethyl- and 2,3,4,7-tetramethylbenzo[*b*]thiophene gives the 6-bromo compound in each case.⁸¹ Treatment of di(3-benzo[*b*]thienyl)methane and 3-(2-benzo[*b*]thienylmethyl)benzo[*b*]thiophene with bromine in chloroform gives a dibromide of

⁴⁷⁹ W. Davies, N. W. Gamble, and W. E. Savige, *J. Chem. Soc.* 4678 (1952).

⁴⁸⁰ R. Montgomery and F. Smith, *J. Chem. Soc.* 258 (1952).

⁴⁸¹ D. A. Shirley, M. J. Danzig, and F. C. Canter, *J. Am. Chem. Soc.* **75**, 3278 (1953).

⁴⁸² R. D. Schuetz, D. D. Taft, J. P. O'Brien, J. L. Shea, and H. M. Mork, *J. Org. Chem.* **28**, 1420 (1963).

⁴⁸³ A. W. Chow, N. M. Hall, J. R. E. Hoover, M. M. Dolan, and R. J. Ferlauto, *J. Med. Chem.* **9**, 551 (1966).

⁴⁸⁴ A. H. Lamberton and J. E. Thorpe, *J. Chem. Soc., C* 2571 (1967).

⁴⁸⁵ R. Gaertner, *J. Am. Chem. Soc.* **74**, 2185 (1952).

undetermined structure in each case.⁴⁸⁶ When 1,1-di(2-benzo[b]-thienyl)ethylene reacts with bromine in carbon disulfide, substitution occurs at one of the ethylenic hydrogens, rather than at a ring hydrogen.¹³²

4,5,6,7-Tetrahydrobenzo[b]thiophene¹⁹³ and several benzo[b]thiophenes containing electron-donating substituents, e.g., 5,6-dimethoxy,¹⁸⁹ 5,6-methylenedioxy,¹⁸⁹ 6-ethoxy,⁴²⁴ 3-methoxy,¹⁸³ and 3-methyl,⁴⁸⁷ are smoothly brominated in the 2-position by *N*-bromosuccinimide in carbon tetrachloride or chloroform in the *absence* of peroxides. Similar treatment of 2-methoxybenzo[b]thiophene gives the 3-bromo derivative.¹⁸³

The halogenation of substituted benzo[b]thiophenes containing other functional groups is discussed in the relevant sections.

b. *By Other Methods.* 5-^{76, 105, 106, 144, 162, 291, 295, 344, 488} and 7-halobenzo[b]thiophenes,^{105, 106, 162, 287, 289, 295, 344, 488} and their 2-methyl,⁷⁶ 3-methyl,^{76, 105, 298, 489-491} and 2,3-dimethyl^{81, 492} derivatives may be prepared by the cyclization processes described in Section IV, B and C. Attempts to prepare 4- and 6-halobenzo[b]thiophenes by analogous reactions invariably lead to a mixture, in which the relative proportion of the two isomers seems to vary from case to case.^{105, 106, 162, 241, 294, 295, 493} The mixtures are usually difficult to separate and, where possible, the components are better prepared by alternative routes.

Chloro-,^{241, 336, 494} bromo-,^{105, 112, 336, 422} iodo-,^{152, 298, 334, 336} and fluorobenzo[b]thiophenes³³⁶ may be obtained in high yields from the appropriate diazonium salt by means of the usual replacement reactions. This method is particularly useful for fluoro- and iodo-

⁴⁸⁶ G. Van Zyl, G. E. Heasley, R. N. Schut, J. W. Van Dyke, and R. G. Korteling, *J. Org. Chem.* **26**, 2916 (1961).

⁴⁸⁷ E. Campaigne and E. S. Neiss, *J. Heterocyclic Chem.* **3**, 46 (1966).

⁴⁸⁸ K. Rabindran, A. V. Sunthakar, and B. D. Tilak, *Proc. Indian Acad. Sci.* **A36**, 405 (1952).

⁴⁸⁹ N. B. Chapman, K. Clarke, and B. Iddon, *J. Chem. Soc.* 774 (1965).

⁴⁹⁰ Smith, Kline & French Lab., British Patent 855,115 (1960); *Chem. Abstr.* **55**, 12423 (1961).

⁴⁹¹ N. B. Chapman, K. Clarke, R. M. Pinder, and S. N. Sawhney, *J. Chem. Soc., C* 293 (1967).

⁴⁹² N. B. Chapman, K. Clarke, D. F. Ewing, and S. D. Saraf, *J. Chem. Soc., C* 197 (1968).

⁴⁹³ S. N. Sawhney, Ph.D. Thesis, University of Hull (1966).

⁴⁹⁴ A. Martani, *Ann. Chim. (Rome)* **47**, 885 (1957).

TABLE VIII
HALOBENZO[*b*]THIOPHENES

Substituents	Melting point and/or boiling point (°C)	Yield (%)	Ref.
2-Cl	34	48	412
2-Br	46	30, 39, 65, 31, 84	478, 564, 406, 112, 183
2-F	(93–94/25 mm)	70	482
2-I	63.4–65	29	413
2,3-Cl ₂	55.5–56.5	83.5, ?, 66 ^a	473, 475, 479
2,3-Br ₂	59	85, 97	477, 107
2-F, 3-Br	21–21.5	51.5	482
2-Br, 3-Me	(121–124/3 mm)	78, 92	487, 485
2-I, 3-Me	?	? ^b	496
2,5-Br ₂	66.5–67.5	62	76
2,3-Br ₂ , 5-NO ₂	216	70	152, 497
2-Br, 3-OMe ^c	(123–125/3 mm)	?	183
2-Br, 6-OEt	75.5–76.5	69	424
2-Br, 5,6-OMe ₂	101–102	91	189
2-Br, 5,6-OCH ₂ O-	161–162	78	189
2-Br, 4,5,6,7-H ₄	(136/14 mm)	60	193
3-Cl	(111–113/10 mm)	52, ?, 32	474, 475, 473
3-Br	(98/0.3 mm)	92, 90, 92	476, 478, 471
3-I	(120–121/1.6 mm)	71, 21	413, 411
3-Br, 2-Me	42–42.5	88, 65	481, 447
3-Br, 7-Me	(112–113/3 mm)	70, 82	78, 478
3-Cl, 2-(2-Naphthyl)	95	92	484
3-I, 2-(2-Naphthyl)	92–93	40	484
3-Br, 2-(2-Naphthyl)	95	85	54

3-Cl, 2-Ph	64	51	245
3-Br, 2-Ph	61-64	98	483
3,5-Br ₂	98-99	78	76
3-Br, 2-OMe ^c	23.5	76	183
3-Cl, 2-CHO	110	90	93
4-Cl	Oil ^d	?	241
4-Br	34-35	21, 12, 21, 15-35 ^e , <i>e</i> , <i>e</i>	105, 422, 422, 344, 105, 162, 294
4-Br, 5-Me	52-53	<i>e</i>	106
4-Br, 3-Me	92-93	11	105
6-Br	57-58	<i>e</i> , <i>e</i> , <i>e</i> ?	105, 162, 294, 315
6-Br, 5-Me	91-92	<i>e</i>	106
6-Br, 3-Me	(138-139/4 mm)	31	105
6-Cl	42-43	70	241
6-Br, 2,3-Me ₂	(174.5/13.5 mm)	77	81
6-Br, 2,3,5-Me ₃	79	78	81
6-Br, 2,3,4,7-Me ₄	73	?	81
7-Cl	(115/10 mm)	40, 50	295, 585
7-Br	(137-138/10 mm)	36, ?, 75, 55-70	105, 162, 488, 344
7-Cl, 3-Me	(110/2 mm)	82	298
7-Br, 3-Me	(129-130/5 mm)	38, 80	105, 298
7-Br, 5-Me	(128-129/5 mm)	71	106
5-Cl	34-36	70, 43	144, 295
5-Br	47	60, 49, 50, 13, ?, 90, 50	144, 291, 344, 488, 162, 315, 315
5-I	54	49	152
5-Cl, 3-Me	32-34	55, 65, ?	489, 298, 490
5-Br, 2-Me	91-92	38	76
5-Br, 3-Me	40-41	31, 31, 70, 47	76, 105, 298, 489
5-Br, 4-Me	45-46	65 ^f	106
5-Br, 6-Me	93-94	65 ^f	106
5-Br, 7-Me	(100-101/3 mm)	72	106
5-F, 3-Me	(94/4 mm)	64	298
5-I, 3-Me	(110-112/1 mm)	50	298
5-Br, 2-Ph	186-187	35	76

continued

TABLE VIII—*continued*

Substituents	Melting point and/or boiling point (°C)	Yield (%)	Ref.
5-Cl, 2,3-Me ₂	80	85, 60–70	81, 492
5-Br, 2,3-Me ₂	100.5	82, 60–70	81, 492
5-Br, 2,3,4,7-Me ₄	97	65	81
5-Cl, 2-CO ₂ Et	74–75	74	336
5-Br, 2-CO ₂ Et	84–85	72	336
5-F, 2-CO ₂ Et	70–72	69	336
5-I, 2-CO ₂ Et	72–73	84	336
4,5,7-F ₃	29–31	80	110
5,6,7-F ₃	31–34	40	110
4,6,7-F ₃	35.5–38	52	110
4,5,6,7-F ₄	49	60, 82	110, 109
4,5,6,7-F ₄ , 2-Me	94.5–95	85	108
4,5,6,7-F ₄ , 3-Me	62–63	74	491

^a Claimed to be 3,5-dichlorobenzo[*b*]thiophene.

^b Characterized as the 1,1-dioxide.

^c Unstable.

^d Characterized as the picrate.

^e A mixture of 4- and 6-isomers was obtained; the percentage recovery of each isomer was rather low.

^f Total yield of a mixture of 4-Me and 6-Me isomers.

benzo[*b*]thiophenes, which are often difficult to prepare by other means. Deamination of the readily available 5-amino-4-bromobenzo[*b*]thiophene affords a convenient route to 4-bromobenzo[*b*]thiophene.⁴²²

The preparation of halobenzo[*b*]thiophenes by reduction of the corresponding thioindoxyl is discussed in Section VI, I, 2; it is of preparative value only in the cases of the otherwise rather inaccessible 6-halo compounds.^{241, 315}

4-Bromo-,^{344, 495} 5-bromo-,³¹⁵ and several polyfluorobenzo[*b*]thiophenes^{109, 110} have been prepared by decarboxylation of the corresponding 2-carboxylic acid with copper and quinoline. Good yields of fluoro compounds are obtained by this method, but those of the bromo compounds are rather low, probably owing to some simultaneous dehalogenation.

2-Halobenzo[*b*]thiophenes are readily obtained from the corresponding 2-benzo[*b*]thienyllithium by the reactions described in Section VII. 2-Iodo-3-methylbenzo[*b*]thiophene is obtained by treatment of the 2-acetoxymercury compound with iodine.⁴⁹⁶

The Hunsdiecker reaction has been used only twice as a potential source of bromobenzo[*b*]thiophenes; with 3-bromo-5-nitrobenzo[*b*]thiophene-2-carboxylic acid it proceeds normally to give 2,3-dibromo-5-nitrobenzo[*b*]thiophene,¹⁵² but with 5-nitrobenzo[*b*]thiophene-2-carboxylic acid the main product is 3-bromo-5-nitrobenzo[*b*]thiophene-2-carboxylic acid, accompanied by smaller amounts of 2,3-dibromo-5-nitrobenzo[*b*]thiophene.^{152, 497}

Halobenzo[*b*]thiophenes are listed in Table VIII.

2. *Properties of Halobenzo[*b*]thiophenes and Their Derived Grignard Reagents*

Bromo- and iodobenzo[*b*]thiophenes readily form Grignard reagents, which react in the usual manner with carbon dioxide^{54, 76, 78, 87, 189, 193, 315, 337, 413, 424, 476, 481, 485, 487} to give carboxylic acids; with ethyl orthoformate^{87, 193} or dimethylformamide⁷⁸ to give aldehydes; with aldehydes,^{469, 471} ketones,^{186, 309, 349, 467, 469, 479, 498} and

⁴⁹⁵ P. Faller, *Compt. Rend.* **C262**, 581 (1966).

⁴⁹⁶ F. G. Bordwell, P. E. Sokol, and J. D. Spainhour, *J. Am. Chem. Soc.* **82**, 2881 (1960).

⁴⁹⁷ M. Martin-Smith and M. Gates, *J. Am. Chem. Soc.* **78**, 5351 (1956).

⁴⁹⁸ F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.* **33**, 3226 (1968).

epoxides^{193, 447, 470, 499, 500} to give alcohols; with nitriles^{344, 478, 495, 501-504} to give ketones; and with-sulfur^{84, 505-507} or selenium⁵⁰⁸ to give mercapto- or hydroselenobenzo[*b*]thiophenes, respectively. 3-Benzo[*b*]thienylmagnesium bromide reacts readily with allyl bromide,⁴⁹⁹ chlorotrimethylsilane,³⁹¹ 2-chloroethyl-*p*-toluenesulfonate,⁵⁰⁹ or 2-dimethylaminoethyl-1-chloroethane⁵¹⁰ to afford 3-allyl-, 3-trimethylsilyl-, 3-(2-chloroethyl)-, and 3-(2-dimethylaminoethyl)benzo[*b*]thiophene, respectively.

Di(3-benzo[*b*]thienyl)methane is obtained by treatment of 3-benzo[*b*]thienylmagnesium bromide with 3-chloromethylbenzo[*b*]thiophene.⁴⁸⁶ Two molecules of 3-benzo[*b*]thienylmagnesium iodide may be coupled by treatment with cupric chloride,³⁰⁵ but not with cupric bromide or nickel bromide,³⁴⁹ to yield 3,3'-di(benzo[*b*]thienyl). A claim³⁴⁹ to have prepared the same compound by the Ullmann reaction is probably not justified.³⁰⁵ The Ullmann reaction otherwise seems to be of general application in the benzo[*b*]thiophene series.^{87, 483}

Halobenzo[*b*]thiophenes^{76, 105, 511} can be selectively metallated in the 2-position by the use of *n*-butyllithium (Section VII).

Bromo-,^{54, 81, 294, 302, 337, 483, 512, 513} and less frequently, chlorobenzo[*b*]thiophenes⁸¹ are readily converted into the corresponding nitriles by heating them with cuprous cyanide in a suitable solvent. 2-Bromobenzo[*b*]thiophene may be smoothly converted into 2-methoxybenzo[*b*]thiophene¹⁸³ or 2-piperidinobenzo[*b*]thiophene⁴⁰⁶ by heating it with sodium methoxide in the presence of cupric oxide

⁴⁹⁹ P. Cagniant and P. Cagniant, *Bull. Soc. Chim. France* 185 (1953).

⁵⁰⁰ P. Cagniant and P. Cagniant, *Bull. Soc. Chim. France* 629 (1952).

⁵⁰¹ P. Faller, *Compt. Rend.* **252**, 1034 (1961).

⁵⁰² P. Faller, *Compt. Rend.* **258**, 2839 (1964).

⁵⁰³ P. Faller, *Compt. Rend.* **260**, 3686 (1965).

⁵⁰⁴ F. A. Vingiello and P. D. Henson, *J. Org. Chem.* **31**, 1357 (1966).

⁵⁰⁵ V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res. (India)* **16B**, 345 (1957).

⁵⁰⁶ C. E. Heyd, Ph.D. Thesis, Michigan State University (1957); *Dissertation Abstr.* **20**, 3490 (1960).

⁵⁰⁷ R. D. Schuetz and C. E. Heyd, *Abstr. Papers 131st Meeting Am. Chem. Soc., Miami* 840 (1957).

⁵⁰⁸ M. Vafai and M. Renson, *Bull. Soc. Chim. Belges* **75**, 145 (1966).

⁵⁰⁹ D. A. Shirley and G. R. Bell, *J. Med. Chem.* **9**, 607 (1966).

⁵¹⁰ P. M. G. Bavin, C. R. Ganellin, J. M. Loynes, P. D. Miles, and H. F. Ridley, *J. Med. Chem.* **9**, 790 (1966).

⁵¹¹ W. Ried and H. Bender, *Chem. Ber.* **89**, 1574 (1956).

⁵¹² M. Martynoff, *Compt. Rend.* **236**, 385 (1953).

⁵¹³ R. B. Mitra, K. Rabindran, and B. D. Tilak, *J. Sci. Ind. Res. (India)* **15B**, 627 (1956).

and potassium iodide, or with piperidine, respectively. Reaction of 3-bromobenzo[b]thiophene with piperidine is very slow, and the main product is the 2-piperidino compound⁴⁰⁶ (Section V, C); reaction with sodium methoxide, however, gives 3-methoxybenzo[b]thiophene almost quantitatively.¹⁸³ The inductive effect of the sulfur atom is believed to be responsible for the somewhat higher reactivity of 2-halobenzo[b]thiophenes toward nucleophiles.⁴⁰⁶

When 4,5,6,7-tetrafluorobenzo[b]thiophene is treated with sodium methoxide, potassium hydroxide in *tert*-butanol, or hydrazine, the fluorine atom in the 6-position undergoes nucleophilic replacement in each case.^{103, 110, 514}

Electrophilic substitution reactions of halobenzo[b]thiophenes are considered in Sections VI, E, 1 (nitration) and VI, L, 2 (Friedel-Crafts acylation).

2-Halobenzo[b]thiophenes are readily dehalogenated by the use of hydrogen in the presence of palladium,^{102, 497} or sodium amalgam in methanol.¹⁰² A 2-halo atom can be selectively removed in the presence of a 3-halo atom, e.g., 2,3-dibromobenzo[b]thiophenes can be converted into the corresponding 3-bromobenzo[b]thiophene with zinc and acetic acid,⁴⁷¹ catalytically,⁷⁷ or by treatment of the 2-lithium derivative with dilute acid.²⁹⁷ 3-Halobenzo[b]thiophenes are unaffected by hydrogen in the presence of palladium,^{102, 484} but they have been successfully dehalogenated by the use of hydriodic acid,⁴⁸⁴ sodium amalgam in methanol,¹⁰² and Raney nickel-hydrazine hydrate,¹⁵² or by the action of ammonium chloride on the corresponding Grignard reagent.⁴⁸⁴ Tin and ethanolic hydrochloric acid causes reductive dehalogenation of 3-iodo-2-(2-naphthyl)benzo[b]thiophene, but not of the corresponding 3-chloro or 3-bromo compounds.⁴⁸⁴

2,3-Dibromobenzo[b]thiophene and its 6-carboxylic acid undergo bisdehalogenation on treatment with sodium hydrazide and hydrazine⁵¹⁵ and on catalytic reduction in alkaline solution,⁷⁷ respectively. Bromonitrobenzo[b]thiophenes readily undergo debromination on treatment with copper and quinoline,⁴¹² copper bronze and benzoic acid,⁸⁴ or tin and hydrochloric acid.⁵¹⁶

⁵¹⁴ R. D. Chambers, J. A. Cunningham, and D. J. Spring, *Tetrahedron* **24**, 3997 (1968).

⁵¹⁵ T. Kauffmann, H. Henkler, and H. Zengel, *Angew. Chem.* **74**, 248 (1962); *Angew. Chem. Intern. Ed. Engl.* **1**, 214 (1962).

⁵¹⁶ P. I. Abramenko and V. G. Zhiryakov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* 227 (1965); *Chem. Abstr.* **63**, 9925 (1965).

A halo atom may be replaced by deuterium by the action of deuterium oxide on the Grignard reagent,^{83, 87, 121} or by reduction of the bromo compound with zinc and deuterated acetic acid.⁸⁹ It has been shown that the first method does not give completely specific deuteration.⁸⁷

3. Preparation of Benzo[b]thiophenes Containing a Halo Atom in a Side Chain

Bromomethylbenzo[b]thiophenes are readily obtained in high yields by treatment of the corresponding methyl compound with *N*-bromosuccinimide in the presence of benzoyl peroxide.^{91, 105, 298, 343, 413, 447, 487, 489-492, 517, 518} Applied to 3-methylbenzo[b]thiophene, this procedure affords 2-bromo-3-methylbenzo[b]thiophene (12%), in addition to the required product; the yield of nuclear substituted product rises to 78% when peroxides are excluded.⁴⁸⁷ When 3,5-dimethylbenzo[b]thiophene is treated with *N*-bromosuccinimide, the 3-methyl group is preferentially brominated,⁴⁸⁹ but in the cases of other 5-alkyl-3-methylbenzo[b]thiophenes inseparable mixtures of products are formed.²⁹² The above reaction has also been applied to 2-benzylbenzo[b]thiophenes, in which cases substitution takes place at a benzylic hydrogen atom.⁵¹⁹

Benzo[b]thiophene^{485, 520-524} and its 2-cyclohexyl,⁴⁸³ 5-methanesulfonyloxy,³³⁷ 5-benzylsulfonyloxy,³³⁷ 7-methyl,⁷⁸ 6-methyl,²⁹² 2-methyl,⁵²⁵ and 5-alkyl²⁹² derivatives are all chloromethylated in the 3-position; the yields depend markedly on the reaction conditions.

⁵¹⁷ Y. Matsuki and K. Fujieda, *Nippon Kagaku Zasshi* **88**, 445 (1967); *Chem. Abstr.* **68**, 59638 (1968).

⁵¹⁸ O. P. Shkurko and V. P. Mamaev, *Izv. Sibirsk. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **81** (1965); *Chem. Abstr.* **64**, 2040 (1966).

⁵¹⁹ American Cyanamid Co., Netherlands Patent Appl. 6,509,177 (1966); *Chem. Abstr.* **66**, 2490 (1967).

⁵²⁰ V. P. Mamaev and O. P. Shkurko, *Zh. Obshch. Khim.* **31**, 3288 (1961); *Chem. Abstr.* **57**, 4622 (1962).

⁵²¹ E. Campaigne and E. S. Neiss, *J. Heterocyclic Chem.* **2**, 231 (1965).

⁵²² N. B. Chapman and A. J. Tompsett, *J. Chem. Soc.* 1291 (1961).

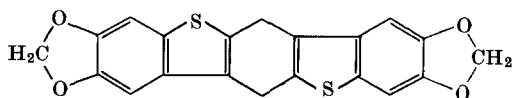
⁵²³ S. Avakian and G. J. Martin, U.S. Patent 2,553,495 (1951); *Chem. Abstr.* **46**, 537 (1952).

⁵²⁴ E. L. Anderson, J. E. Casey, L. C. Greene, J. J. Lafferty, and H. E. Reiff, *J. Med. Chem.* **7**, 259 (1964).

⁵²⁵ W. Fruhstorfer and H. Mueller-Calgan, German Patent 1,121,054 (1962); *Chem. Abstr.* **57**, 835 (1962).

3-Methylbenzo[*b*]thiophene is chloromethylated in the 2-position.⁵²⁶ 2- and 3-iodobenzo[*b*]thiophene do not undergo chloromethylation.⁴¹³ Attempted chloromethylation of 5,6-methylenedioxybenzo[*b*]thiophene gives a halogen-free solid of high molecular weight, to which a structure has not yet been assigned.¹⁹⁰ 2,3-Di(chloromethyl)benzo[*b*]thiophene is obtained by continued chloromethylation of benzo[*b*]thiophene.⁵¹¹ Benzo[*b*]thiophene undergoes 2,3-dibromomethylation when treated with *sym*-dibromomethyl ether, or with hydrogen bromide, acetic acid, and paraformaldehyde.⁵²⁷ Dihalomethylation does not proceed satisfactorily when the nucleus already contains a halo atom.⁴⁹²

Chloromethyl-,^{87, 336, 526, 528} bromomethyl-,^{77, 496, 518, 527} and other side-chain halobenzo[*b*]thiophenes^{193, 439, 447, 486, 498-500, 529} may be obtained in high yield from the corresponding alcohol (Section VI, J).



(166)

Treatment of 2-hydroxymethyl-5,6-methylenedioxybenzo[*b*]thiophene with thionyl chloride, and attempted crystallization of the product from ethanol, gives a mixture of the 2-ethoxymethyl compound and the compound **166**.¹⁹⁰ The mechanism of this reaction has been discussed.¹⁹⁰

2- and 3-(2-chloroethyl)benzo[*b*]thiophene are conveniently obtained by the action of 2-chloroethyl-*p*-toluenesulfonate on 2-benzo[*b*]thienyllithium and 3-benzo[*b*]thienylmagnesium bromide, respectively.⁵⁰⁹ 2-(2-Iodoethyl)benzo[*b*]thiophene is obtained by treatment of the corresponding chloro compound with sodium iodide in acetone.⁵²⁹

4. Properties of Benzo[*b*]thiophenes Containing a Halo Atom in a Side Chain, and Their Derived Grignard Reagents

Side-chain halobenzo[*b*]thiophenes undergo most of the expected nucleophilic replacement reactions. Replacement by the cyanide

⁵²⁶ R. Gaertner, *J. Am. Chem. Soc.* **74**, 2991 (1952).

⁵²⁷ W. Ried and J. Grabosch, *Chem. Ber.* **91**, 2485 (1958).

⁵²⁸ R. Gaertner, *J. Am. Chem. Soc.* **74**, 766 (1952).

⁵²⁹ D. B. Capps and C. S. Hamilton, *J. Am. Chem. Soc.* **75**, 697 (1953).

group^{524, 525, 530} is best accomplished by the use of an alkali metal cyanide in aqueous acetone^{77, 337, 473, 531} or aqueous ethanol.^{337, 447, 521} Addition of a small amount of sodium iodide may increase the yields.^{485, 517} Yields tend to be very variable when ethanol is used as solvent, since replacement of the halo atom by the ethoxyl group is a competing reaction⁵³¹ and, in cases in which dehydrohalogenation is possible, a high yield of olefin may be formed.⁴⁹⁹ 3-Chloromethylbenzo-[b]thiophene reacts with methanolic potassium cyanide to give mainly 3-methoxymethylbenzo[b]thiophene.^{473, 532} Treatment of 3-chloromethylbenzo[b]thiophene with sodium cyanide in dimethylsulfoxide gives 2-cyano-3-methylbenzo[b]thiophene (2%) in addition to 3-cyanomethylbenzo[b]thiophene.⁵²¹ The chlorine atom in chloromethylbenzo[b]thiophenes may be replaced by the hydroxyl,⁴¹⁹ acetoxyl,^{337, 527} or thiocyanate⁴⁷³ group by the usual reactions. The solvolysis of (2- or 3-benzo[b]thienyl)phenylmethyl chloride has been studied.^{533, 534}

The reactions of halomethylbenzo[b]thiophenes with amines are discussed in Section VI, H, 2.

Most side-chain halobenzo[b]thiophenes react normally with diethyl sodiomalonate^{439, 447, 490, 500, 535} and its *C*-alkyl derivatives,^{499, 536} but elimination may predominate in the case of a secondary halo compound.⁴⁹⁹ Halomethylbenzo[b]thiophenes react normally with potassium phthalimide in the Gabriel reaction (Section VI, H, 2). Where dehydrohalogenation is possible, alcoholic potassium hydroxide gives the corresponding olefin in good yield.⁴⁶⁹

Halomethylbenzo[b]thiophenes form salts with hexamethylene-tetramine,^{78, 91, 105, 144, 343, 487, 520, 537} pyridine,^{77, 144, 511} and triphenylphosphine.⁴⁶⁵

3-Chloromethylbenzo[b]thiophene may be oxidized to the corre-

⁵³⁰ E. Merck A.-G., French Patent M1614 (1963); *Chem. Abstr.* **58**, 12574 (1963).

⁵³¹ I. Jirkovský and M. Protiva, *Collection Czech. Chem. Commun.* **28**, 2582 (1963).

⁵³² A. H. Schlesinger, U.S. Patent 2,692,884 (1954); *Chem. Abstr.* **49**, 14810 (1955).

⁵³³ M. W. Hanson, Ph.D. Thesis, University of Houston (1964); *Dissertation Abstr.* **25**, 2230 (1964).

⁵³⁴ M. W. Ruchelman, Ph.D. Thesis, University of Houston (1963); *Dissertation Abstr.* **24**, 1837 (1963).

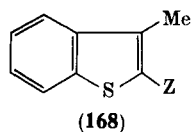
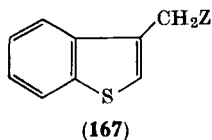
⁵³⁵ W. H. Edgerton, U.S. Patent 2,916,495 (1959); *Chem. Abstr.* **54**, 5694 (1960).

⁵³⁶ N. V. Bac, N. P. Buu-Hoï, and N. D. Xuong, *Compt. Rend.* **254**, 3555 (1962).

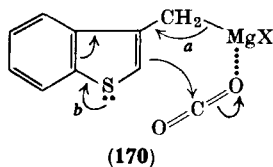
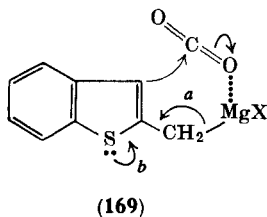
⁵³⁷ V. V. Ghaisas, *J. Org. Chem.* **22**, 703 (1957).

sponding aldehyde.^{337, 483} Reduction of 3-chloromethylbenzo[b]thiophene with stannous chloride in hydrochloric acid affords 3-methylbenzo[b]thiophene (59%) and a by-product (20%), which is probably 3-methyl-2-(3-benzo[b]thienylmethyl)benzo[b]thiophene.⁴⁸⁵ Reduction with lithium aluminum hydride–lithium hydride increases the yield of 3-methylbenzo[b]thiophene to 92%.⁵²⁶ Lithium aluminum hydride alone causes hydrogenolyses of side-chain halobenzo[b]thiophenes.⁴⁸⁶

Conventional procedures for the preparation of Grignard reagents from 2- or 3-chloromethylbenzo[b]thiophene give large amounts of coupling product, but coupling is minimized by the entrainment procedure.^{413, 485, 526, 528} Treatment of 2-benzo[b]thienylmethylmagnesium chloride with carbon dioxide, acetyl chloride, formaldehyde, or ethyl benzoate leads exclusively to products in which the oxygen-containing function is present in the 3-position, and a methyl group remains in the 2-position.⁵²⁸ Mixtures of normal (**167**) and abnormal products (**168**) are formed when 3-benzo[b]thienylmethylmagnesium



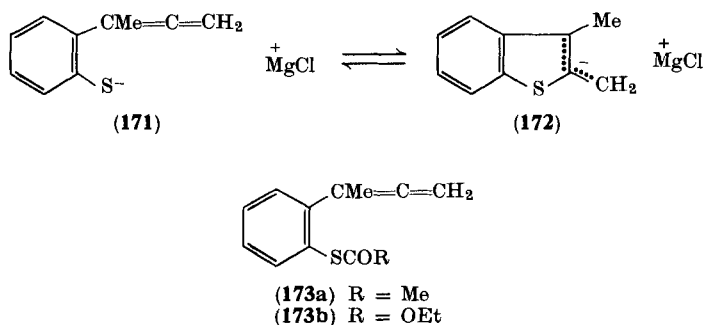
chloride reacts with carbon dioxide ($Z = \text{CO}_2\text{H}$), formaldehyde ($Z = \text{CH}_2\text{OH}$), or ethylene oxide ($Z = \text{CH}_2\text{CH}_2\text{OH}$).⁴⁸⁵ Ethyl chloroformate gives exclusively the abnormal product (**168**; $Z = \text{CO}_2\text{Et}$).⁴⁸⁵ 2- and 3-benzo[b]thienylmethylmagnesium chloride react normally with hindered ketones such as 1-benzoyl-2,3,5,6-tetramethylbenzene.^{485, 528} The tendency of 2-benzo[b]thienylmethylmagnesium chloride to undergo “abnormal” reactions more readily than the



3-isomer has been discussed in terms of the mechanisms **169** and **170** (using the reaction with carbon dioxide as an example).⁴⁸⁵ Shift a,

which favors the "abnormal" reaction, is aided in each case by shift b. However, shift b will be of more assistance in the case of the 2-isomer (**169**), since it can take place without involving the resonance system of the benzene ring.⁴⁸⁵

2-Bromo-3-benzo[*b*]thienylmethylmagnesium chloride reacts with formaldehyde or ethyl chloroformate to give only the coupling product [1,2-di(2-bromo-3-benzo[*b*]thienyl)ethane] and polymeric material.⁴¹³ When 2-chloromethyl-3-methylbenzo[*b*]thiophene reacts with magnesium in the conventional manner, 1,2-di(3-methyl-2-benzo[*b*]thienyl)ethane is formed in excellent yield.⁵²⁶ By using the entrainment technique, the equilibrium mixture (**171** and **172**) is obtained, in which only a trace of the normal Grignard reagent (**172**) is present.



When the mixture (**171** and **172**) reacts with carbon dioxide, acetyl chloride, or ethyl chloroformate, the main products (derived from **171**) are 2,3-dimethylbenzo[*b*]thiophene, **173a**, and **173b**, respectively, together with a trace of "normal" product (derived from **172**) in each case. Attempted hydrolysis of **173a** or **173b** with ethanolic alkali yields 2,3-dimethylbenzo[*b*]thiophene in excellent yield in each case, thus demonstrating the lability of the parent *o*-(α -methylallenyl)-thiophenol.⁵²⁶ 2-Chloromethylbenzofuran,⁵²⁶ but not 2-chloromethylbenzo[*b*]thiophene,⁵²⁸ undergoes analogous cleavage reactions. It is therefore somewhat surprising that the methyl group in 2-chloromethyl-3-methylbenzo[*b*]thiophene should promote cleavage, even though the hyperconjugative and inductomeric electron release of the methyl substituent should operate in the required direction.⁵²⁶

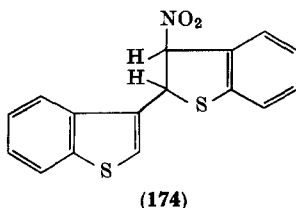
When 4-, 5-, 6-, or 7-benzo[*b*]thienylmethylmagnesium bromide reacts with carbon dioxide, the yield of the corresponding benzo[*b*]-

thienylacetic acid is only *ca.* 1%, except in the case of the 4-substituted compound, where it is 35%.⁵¹⁷ The coupling product predominates (30–40%) in each case; no “abnormal” products are obtained, and the reactivity is similar to that of a benzylmagnesium halide. The coupling products are obtained in higher yields by reaction of the corresponding bromomethylbenzo[*b*]thiophene with phenyllithium.⁵¹⁷

E. NITRO COMPOUNDS

1. Preparation

a. *By Direct Nitration.* Mononitration of benzo[*b*]thiophene gives a rather complex mixture of products, the constitution of which depends markedly on the nitration conditions. In all cases, however, the 3-isomer predominates.^{68, 84, 230, 412, 479, 538, 539} Nitration in acetic anhydride at 25° gave a 73% yield of 3-nitrobenzo[*b*]thiophene; no further products were isolated but the presence of 16% of the 5-isomer could be detected spectroscopically, together with other unspecified isomers.⁶⁸ With concentrated nitric acid in acetic acid at 10°, 47–55% of 3-nitrobenzo[*b*]thiophene was obtained,^{84, 538} together with 43 and 9% of the 4- and 6-isomer, respectively; no 5-isomer could be detected.⁸⁴ The mixture obtained by reaction of benzo[*b*]thiophene with fuming nitric acid in acetic acid at 60–70° has not been resolved, but has been shown to contain 10–15% of the 2- and 60–65% of the 3-nitro isomer, and 20–30% of other nitro compounds, mainly 4-nitrobenzo[*b*]thiophene.^{412, 539} The yield of the 3-nitro isomer falls as the temperature is lowered,⁴⁷⁹ owing to the competitive formation of the dimeric compound (174).⁴¹²



⁵³⁸ W. Davies and Q. N. Porter, *J. Chem. Soc.* 826 (1957).

⁵³⁹ G. Van Zyl, J. W. Van Dyke, V. L. Heasley, D. C. De Jongh, C. J. Bredeweg, and D. C. Neckers, *4th Ann. Rept. Res., Petrol. Res. Fund., Am. Chem. Soc.* 39 (1959).

Considerable work is still to be done on the separation of the mixtures frequently arising in the nitration of benzo[*b*]thiophenes; most workers have referred to, and isolated, only the major isomer of the nitration mixture. Nitration of 2-methyl-,⁴⁸¹ 7-methyl-,⁷⁸ 2-(2-naphthyl)-,⁵⁴ and 2-acetoxymethylbenzo[*b*]thiophene⁵¹⁸ gives the 3-nitro compound in each case. 2-Bromobenzo[*b*]thiophene gives a mixture, in which the 4-, 6-, 5-, or 7- and probably the 3-nitro compounds are present.⁴¹² Three crystalline compounds obtained from the mixture have not yet been identified.⁴¹² An electron-withdrawing group in the 2-position directs the nitro group mainly into the benzene ring.^{141, 412} Benzo[*b*]thiophenes with electron-donating substituents in the 3-position [e.g., 3-methyl,^{162, 481, 540} 3-acetamido (and its 5-chloro and 5-bromo derivatives),¹¹⁷ and 3-morpholino⁵⁴¹] are nitrated almost exclusively in the 2-position. Nitration of 3-bromobenzo[*b*]thiophene gives 3-bromo-2-nitrobenzo[*b*]thiophene (90%)^{84, 412} and its 4-nitro isomer (10%).⁸⁴ The products formed by nitrating a mixture of potassium 2- and 3-benzo[*b*]thiophene sulfonate may be desulfonated to yield a mixture of 3-, 4-, 6-, and 7-nitrobenzo[*b*]thiophene. The composition of the mixture depends on the nitrating conditions. Nitration in phosphoric acid gives mainly the 4-nitro compound (50–69%), whereas in sulfuric acid at 50–90° it gives mainly (60%) the 6-isomer.⁸⁴ 3-Nitrobenzo[*b*]thiophene is not attacked by fuming nitric acid in glacial acetic acid at 105°^{99, 412}; it is, however, nitrated with 1 mole of potassium nitrate in concentrated sulfuric acid at 0–4°.^{84, 99, 538, 542} The mixture that arises has recently been separated and shown by chemical and spectroscopic methods to contain the previously well-characterized^{84, 538, 542} 3,4-dinitrobenzo[*b*]thiophene, 3,5-, 3,6-, and 3,7-dinitro- and 3,4,6-trinitrobenzo[*b*]thiophene, and some polymeric material.⁹⁹ Nitration of benzo[*b*]thiophenes possessing other electron-withdrawing groups in the 3-position gives a mixture of products in which the nitro group is always confined to the benzene ring. Despite the *peri* interaction, substitution is most favored in the 4-position, then in the 6-, and last in the 5- or 7-position.⁹⁹

⁵⁴⁰ A. Ricci, *Ann. Chim. (Rome)* **43**, 323 (1953).

⁵⁴¹ G. Van Zyl, D. C. De Jongh, V. L. Heasley, and J. W. Van Dyke, *J. Org. Chem.* **26**, 4946 (1961).


⁵⁴² K. Fries, H. Heering, E. Hemmecke, and G. Siebert, *Ann. Chem.* **527**, 83 (1937).

⁵⁴³ J. Bolssens, J. A. C. T. Brouwers, J. H. Choufoer, A. Kats, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.* **73**, 819 (1954).

Nitration of 2,3-dimethylbenzo[b]thiophene unexpectedly gives 3-methyl-2-nitromethylbenzo[b]thiophene as the major product (33%), together with 2,3-dimethyl-6-nitrobenzo[b]thiophene (10%),

TABLE IX

NITRATION OF BENZO[b]THIOPHENE AND ITS DERIVATIVES^a

Starting material (substituents)	Position of entry of nitro group	Melting point of product (°C)	Yield (%)	Ref.
—	3-NO ₂ ^b	79	55, 47	479, 84
	—	—	73, 55	68, 538
2-Me	3-NO ₂	98–98.5	48	481
2-(2-Naphthyl)	3-NO ₂	144	52	54
2-CH ₂ OAc	3-NO ₂	106–107.5	30	518
3-Me	2-NO ₂	148–149	25, —	481, 540
	2-NO ₂	165–166.5	—	541
3-NHAc	2-NO ₂	208–209	80	117
3-NHAc, 5-Cl	2-NO ₂	218–222	74	117
3-NHAc, 5-Br	2-NO ₂	238–239	75	117
3-NO ₂	4-NO ₂	199–200	31, 32	99, 538, 542
	5-NO ₂	169–170	4.2	99
	6-NO ₂	172–173	53.7	99
	7-NO ₂	183–184	11.5	99
	4,6-diNO ₂	206–207	—	99
2,3-Me ₂	6-NO ₂	124–125	10	100
	2-CH ₂ NO ₂ , 3-Me	103–104	33	
2,3-Br ₂	4-NO ₂	139–140	37	101
	6-NO ₂	154–156	41	
5-OH	4-NO ₂	119	47	152
5-NHAc	4-NO ₂	131–132	70	422
5-OCOPh	3-NO ₂	180–180.5	69	152
5-NHAc, 2-CO ₂ H	4-NO ₂	254.5–256	65	497
5-OH, 3-Br	4-NO ₂ ^c	160	59	152
5-OH, 4,6-Br ₂	4-NO ₂ ^d	128–130	43	152, 421
5-OH, 4-Br	6-NO ₂	175–176	58	152
5-OH, 2-CO ₂ H	4-NO ₂	273	61	152
5,6-OCH ₂ O-	<i>x</i> -NO ₂	235–236	98	548
7-Me	3-NO ₂	117–118	57	78

^a Excluding carboxylic acids, aldehydes, and ketones (see appropriate sections).

^b Other isomers were formed, but were not isolated.

^c With excess of nitric acid a dinitro compound, m.p. 211°–213°C, was readily formed.

^d 4,6-Dibromo-4-nitro-5-oxo-4,5-dihydrobenzo[b]thiophene was formed as a crystalline intermediate.

and 3-methylbenzo[*b*]thiophene-2-carboxaldehyde (6%).¹⁰⁰ 2,3-Dibromobenzo[*b*]thiophene undergoes nitration in the 4- and 6-position.¹⁰¹

The above results are summarized in Table IX; the nitration of benzo[*b*]thiophenes containing other functional groups is discussed in the appropriate sections.

b. *By Other Methods.* 2-Nitrobenzo[*b*]thiophene may be prepared by decarboxylation of the corresponding 3-carboxylic acid,⁸⁴ or more conveniently, by debromination of 3-bromo-2-nitrobenzo[*b*]thiophene.^{84, 412}

4-Nitrobenzo[*b*]thiophene may be prepared by reaction of the 3,4-dinitro compound with alcoholic ammonium sulfide^{99, 422, 538}; other workers have claimed that this method yields only traces of the desired product.⁸⁴ It may also be prepared by deamination of 5-amino-4-nitrobenzo[*b*]thiophene,^{162, 422} or by decomposition of 4-benzo[*b*]thiophene diazonium cobaltinitrite with aqueous sodium nitrite in the presence of cuprous oxide and cupric sulfate.⁸⁴ 7-Nitrobenzo[*b*]thiophene may be obtained by the latter method (15% yield) from the corresponding amine.⁸⁴

5-Nitrobenzo[*b*]thiophene is obtained in 10% yield by the cyclization of (*p*-nitrophenylthio)acetaldehyde dimethyl acetal (Section IV, B); 7-nitrobenzo[*b*]thiophene cannot be prepared by this method.⁴⁸⁸ 5-Nitrobenzo[*b*]thiophene^{84, 218, 338, 422, 538, 543-545} and its 3-phenyl,³³³ 3-methyl,²⁹⁸ 3,6-dimethyl,³³⁰ and 7-nitro-3-phenyl³³⁴ derivatives may be obtained most conveniently by decarboxylation of the readily available (Section IV, D) 2-carboxylic acids. 5-,^{494, 546} 6-,^{494, 546} and 7-⁴⁹⁴ nitro-3-acetoxybenzo[*b*]thiophene may be prepared almost quantitatively by cyclization reactions (Section IV, D).

2. Properties

Reduction of 2-nitrobenzo[*b*]thiophene with ethanolic ammonium sulfide gives thiooxindole.⁸⁴ Reduction of other nitro compounds to the corresponding amines is discussed in Section VI, F.

A nitro group activates toward nucleophilic replacement of a halo atom^{412, 541} or an amino group^{152, 497} in an adjacent ring position.

⁵⁴⁴ O. Dann and M. Kokorudz, *Chem. Ber.* **91**, 181 (1958).

⁵⁴⁵ V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* 166 (1967); *Chem. Abstr.* **67**, 64268 (1967).

⁵⁴⁶ N. S. Dokunikhin and Yu. E. Gerasimenko, *Zh. Obshch. Khim.* **30**, 635 (1960); *Chem. Abstr.* **54**, 21763 (1960).

5-Nitrobenzo[*b*]thiophene undergoes bromination¹⁵² and Friedel-Crafts acetylation⁴²³ in the 3-position.

F. AMINES

1. 2-Aminobenzo[*b*]thiophenes

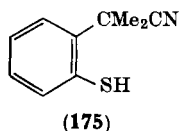
The rather unstable 2-aminobenzo[*b*]thiophene has recently been obtained by the successive mild hydrolysis and decarboxylation of ethyl 2-acetamidobenzo[*b*]thiophene-3-carboxylate^{114, 441} and by cyclization of the nitrile (68a).^{112, 285, 547} 2-Amino-3-methylbenzo[*b*]thiophene¹¹³ and 2,3-dihydro-3,3-dimethyl-2-iminobenzo[*b*]thiophene (14)^{113, 285} have been similarly prepared from 68b and 68c, respectively (Section IV, A). Previously, only derivatives of 2-aminobenzo[*b*]thiophene had been isolated. Thus, reduction of 3-bromo-2-nitrobenzo[*b*]thiophene with tin and hydrochloric acid gives 2-aminobenzo[*b*]thiophene hydrochloride⁵¹⁶ and catalytic reduction of 3-methyl-2-nitrobenzo[*b*]thiophene⁴⁸¹ or 3-acetamido-2-nitrobenzo[*b*]thiophene,¹¹⁷ followed by immediate acetylation of the crude product, gives the corresponding 2-acetamido compound. 5-Bromo-⁷⁶ and 3-methyl-2-acetamidobenzo[*b*]thiophene¹⁰² may be prepared from the corresponding 2-acetylbenzo[*b*]thiophene by the Schmidt reaction. 2-Acetamido-5,6-methylenedioxybenzo[*b*]thiophene may be prepared from the 2-carboxamide by the Hofmann reaction, followed by acetylation of the resulting unstable amine.⁵⁴⁸ An acetamido-5,6-methylenedioxybenzo[*b*]thiophene of undetermined structure has also been prepared from the corresponding nitro compound.⁵⁴⁸ Heating 2-bromobenzo[*b*]thiophene with piperidine in a sealed tube gives a good yield (85%) of 2-piperidinobenzo[*b*]thiophene.⁴⁰⁶ The same product is formed in much lower yield (20%) by more vigorous treatment of 3-bromobenzo[*b*]thiophene with piperidine (Section V, C).⁴⁰⁶ Thioxindole will react with aniline (but not with other aromatic amines) to yield 2-*N*-phenylaminobenzo[*b*]thiophene (Section VI, I, 1).⁵⁴¹ It is also obtained by decarboxylation of 2-aminobenzo[*b*]thiophene-3-carboxylic acid in the presence of aniline.¹¹⁴

The chemical behavior of 2-aminobenzo[*b*]thiophene is consistent with that of an aromatic heterocyclic amine: it forms Schiff's bases

⁵⁴⁷ *Chem. Eng. News* **43**, 45 (1965).

⁵⁴⁸ E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.* **26**, 1327 (1961).

with aromatic aldehydes and it can be diazotized.¹¹² The diazonium salt will not couple with 2-naphthol, but the diazo group can be replaced normally by bromine or hydroxyl.¹¹² The existence of 2-aminobenzo[*b*]thiophenes as the amino, and not as the imino, tautomer has been demonstrated by spectroscopic measurements (Section III, B)¹¹²; its oxygen analog (thiooxindole) exists solely in the oxo form.¹¹² The behavior of 2-amino-3-methylbenzo[*b*]thiophene is very different from that of the imino compound (**14**).¹¹³ For example, although **14** and 2-amino-3-methylbenzo[*b*]thiophene both



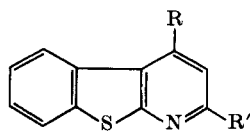
form hydrochlorides and *N*-acetyl derivatives, only the latter reacts with benzaldehyde to form a Schiff's base.¹¹³

The imino compound (**14**) is stable under acidic conditions, but under alkaline conditions it appears to behave as the ring-chain tautomer (**175**) and undergoes ring opening to give chain derivatives. Thus, it yields the disulfide from **175** when treated with alkaline hydrogen peroxide and the sulfide (**68c**) when treated with benzyl chloride and sodium ethoxide.¹¹³

In keeping with their aromatic stability, 2-aminobenzo[*b*]thiophene and its 3-methyl derivative do not undergo such ring-opening reactions.¹¹² Acidic hydrolysis of 2-amino-^{112, 113, 406, 441} or 2-imino-benzo[*b*]thiophene¹¹³ derivatives and vigorous alkaline hydrolysis of ethyl 2-acetamidobenzo[*b*]thiophene-3-carboxylate¹¹⁴ yield the corresponding thiooxindole. Di(2-benzo[*b*]thienyl)amine is formed when 2-aminobenzo[*b*]thiophene is heated in the presence of a trace of acetic acid.¹¹⁴

Reaction of 2-aminobenzo[*b*]thiophene stannichloride with methyl vinyl ketone in the presence of ferrous chloride and zinc chloride yields 4-methyl[1]benzothieno[2,3-*b*]pyridine (**176a**).⁵¹⁶ Reaction of the plumbichloride complex of 2-aminobenzo[*b*]thiophene hydrochloride with the diethyl acetal of acetoacetaldehyde in the presence of zinc chloride affords **176b**.⁵⁴⁹ The pyridine derivative (**176c**) is obtained

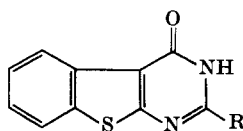
⁵⁴⁹ V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* 334 (1965); *Chem. Abstr.* **63**, 13231 (1965).



(176a) R = Me, R' = H

(176b) R = H, R' = Me

(176c) R = R' = Me



(177)

by treatment of 2-aminobenzo[b]thiophene with acetylacetone in the presence of phosphoric acid.¹¹⁴

Amino derivatives of 4,5,6,7-tetrahydrobenzo[b]thiophene are discussed in Section VI, B, 4.

The pyrimidine derivative (177; R = Me) is obtained by dehydrogenation of 2-acetamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide.¹¹⁴ The related compound (177; R = H) is obtained by treatment of ethyl 2-aminobenzo[b]thiophene-3-carboxylate with formamide.¹¹⁴

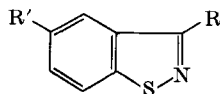
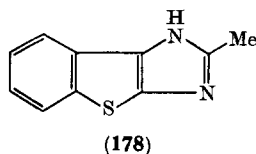
2. 3-Aminobenzo[b]thiophenes

3-Aminobenzo[b]thiophene is apparently less stable than its 2-isomer, and is usually characterized as a salt or an acyl derivative.⁵⁵⁰

The crystalline product obtained by reducing 3-nitrobenzo[b]thiophene with alcoholic ammonium sulfide has not been analyzed, but spectral data suggest that it may be 3-aminobenzo[b]thiophene.⁸⁴ Similar reduction of 2-nitrobenzo[b]thiophene gives thioxindole.⁸⁴ 3-Acetamidobenzo[b]thiophene and its 5-chloro or 5-bromo derivative are conveniently prepared by Beckmann rearrangement of the oxime of the appropriate 3-acetylbenzo[b]thiophene.¹¹⁷ 2-Methyl-⁴⁸¹ and 7-methyl-3-acetamidobenzo[b]thiophene⁷⁸ are obtained by immediate acetylation of the crude product from the reduction of the corresponding nitro compound. 3-Amino-2-(2-naphthyl)benzo[b]thiophene is quite stable in the free form, and is obtained either by reduction of the corresponding 3-nitro compound or by the Hofmann reaction on the corresponding 3-carboxamide.⁵⁴ Schmidt rearrangement of 2-methyl-¹⁰² or 5-bromo-3-acetylbenzo[b]thiophene⁷⁶ affords the corresponding acetamido compound in good yield.

2,3-Diacetamidobenzo[b]thiophene is cyclized in low yield to the imidazole derivative (178) by hot 2 *N* hydrochloric acid.¹¹⁷ When

⁵⁵⁰ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 52. Wiley (Interscience), New York, 1954.

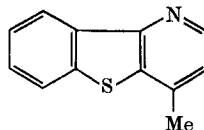


(179a) R = CN, R' = H

(179b) R = CONH₂, R' = H

(179c) R = CN, R' = Br or Cl

(179d) R = CONH₂, R' = Br or Cl



3-acetamido-2-nitrobenzo[*b*]thiophene and its 5-chloro or 5-bromo derivative are heated at 225° with ferrous oxalate, a mixture of 3-cyano-1,2-benzisothiazole (179a) and 1,2-benzisothiazole-3-carboxamide (179b) or of their respective 5-halo derivatives (179c and 179d) is obtained.¹¹⁷ The benzothienopyridine (180) is obtained by reaction of 3-aminobenzo[*b*]thiophene stannichloride with methyl vinyl ketone in the presence of ferrous chloride and zinc chloride.⁵¹⁶ Heating 3-acetamidobenzo[*b*]thiophenes with phosphorus pentasulfide converts them into the corresponding 3-thioacetamido compounds.^{551, 552}

N-Substituted 3-aminobenzo[*b*]thiophenes are readily obtained by heating thioindoxyl with the appropriate primary or secondary aromatic amine,^{539, 541, 553, 554} or primary aliphatic amine⁵⁴¹ (Section VI, I, 2). 3-*N,N*-Dialkylaminobenzo[*b*]thiophenes are best obtained by reaction of 3-bromobenzo[*b*]thiophene-1,1-dioxide with a secondary aliphatic amine, followed by reduction of the product with lithium aluminum hydride (Section VI, P, 2, *f*).⁵⁴¹ 3-Amino-2-nitrobenzo[*b*]thiophene and its *N*-substituted derivatives are conveniently obtained

⁵⁵¹ Z. I. Miroshnichenko and M. A. Al'perovich, *Zh. Obshch. Khim.* **32**, 1245 (1962); *Chem. Abstr.* **58**, 2442 (1963).

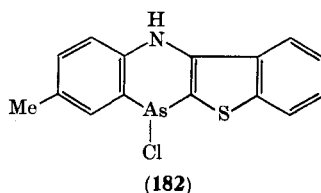
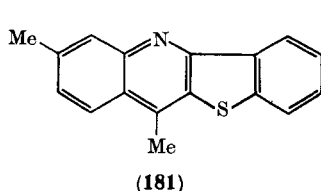
⁵⁵² M. A. Al'perovich and Z. I. Miroshnichenko, U.S.S.R. Patent 124,447 (1959); *Chem. Abstr.* **54**, 11051 (1960).

⁵⁵³ N. P. Buu-Hoi, V. Bellavita, A. Ricci, J. P. Hoeffinger, and D. Balucani, *J. Chem. Soc.* **2646** (1965).

⁵⁵⁴ N. P. Buu-Hoi, V. Bellavita, A. Ricci, J. P. Hoeffinger, and D. Balucani, *J. Chem. Soc., C* **47** (1966).

by heating 3-bromo-2-nitrobenzo[*b*]thiophene with ammonia or the appropriate primary or secondary amine.^{412, 541} *N*-Substituted 3-aminobenzo[*b*]thiophenes undergo electrophilic substitution in the 2-position.⁵⁴¹

3-Aminobenzo[*b*]thiophenes normally exist almost entirely in the amino form in the solid phase or in chloroform solution^{84, 115, 412, 541}; a claim that the imino form of 3-anilinobenzo[*b*]thiophene predominates in trifluoroacetic acid solution,¹¹⁵ was made by authors who failed to realise that a cation is formed under these conditions.



3-Anilino-⁵⁵³ and the three 3-tolylaminobenzo[*b*]thiophenes⁵⁵⁴ undergo the Berntsen reaction when heated with an aliphatic carboxylic acid anhydride and zinc chloride to yield polycyclic compounds (e.g., **181** from 3-*m*-tolylaminobenzo[*b*]thiophene and acetic anhydride). They give analogous arsenic derivatives (e.g., **182** from 3-*p*-tolylaminobenzo[*b*]thiophene) when heated with arsenic trichloride in *o*-dichlorobenzene.^{553, 554}

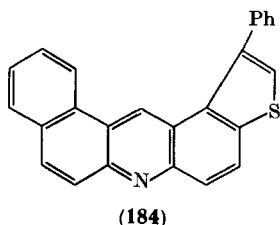
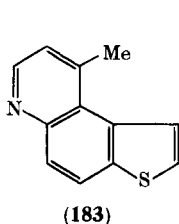
3. 4-Aminobenzo[*b*]thiophenes

4-Aminobenzo[*b*]thiophene has been prepared by catalytic reduction of 4-nitrobenzo[*b*]thiophene,^{84, 422} by heating 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one oxime with acetic acid and acetic anhydride in the presence of hydrogen chloride,^{105, 241} and by means of the Bucherer reaction with 4-hydroxybenzo[*b*]thiophene.⁸⁴ The amino group may be diazotized, and hence replaced by the bromo,¹⁰⁵ chloro,²⁴¹ hydroxy,⁴²² or nitro⁸⁴ group by the usual methods. 4-Aminobenzo[*b*]thiophene is also converted into 4-hydroxybenzo[*b*]thiophene by reaction with hot 15% phosphoric acid.⁸⁴ Reduction of substituted 5-hydroxy-4-nitro-^{152, 421, 497} and 5-hydroxy-4-nitrosobenzo[*b*]thiophenes⁴⁹⁷ gives the corresponding hydroxy amine, which readily undergoes oxidation to the unstable 4,5-quinone (Section VI, K, 2).

4. 5-Aminobenzo[*b*]thiophenes

5-Aminobenzo[*b*]thiophene and its simple ring-substituted derivatives are most conveniently obtained by reduction of the corresponding nitro compound with tin and hydrochloric acid,^{333, 334, 544, 545} iron and hydrochloric acid,⁵⁵⁵ ferrous sulfate and ammonia,^{185, 330, 333, 334, 497} sodium borohydride and palladized charcoal,³³⁷ catalytically,^{152, 422, 488, 543} or, preferably, with Raney nickel and hydrazine hydrate.^{152, 298, 338, 497, 556} Several 5-aminobenzo[*b*]thiophenes may also be made by cyclization reactions (Section IV, D).^{239, 330, 331, 333, 494}

The amino group of 5-aminobenzo[*b*]thiophene and its derivatives can be diazotized, and subsequently replaced by the following groups: hydrogen,^{185, 315, 422} chloro, bromo, fluoro,³³⁶ iodo,^{152, 298, 336} cyano,⁵⁵⁷ hydroxyl,^{337, 497, 558} mercapto,⁵⁴⁴ hydroseleno,⁵⁰⁸ and thiocyanato.³³² Ethyl 5-aminobenzo[*b*]thiophene-3-carboxylate is converted into the 5-isocyanato compound on treatment with carbonyl chloride in ethyl acetate.⁵⁵⁵ 5-Aminobenzo[*b*]thiophene-2-carboxylic acid is best converted into the corresponding 5-hydroxy compound by means of the Bucherer reaction.^{152, 338} Heating 5-aminobenzo[*b*]thiophene at 240° with its hydrochloride affords di(5-benzo[*b*]thienyl)amine.¹⁵² 9-Methylthieno[3,2-*f*]quinoline (**183**) is obtained by reaction of 5-aminobenzo[*b*]thiophene hydrochloride with methyl vinyl ketone in the presence of zinc chloride.⁵⁴⁵ The 7-methyl isomer of **183** is obtained by heating 5-aminobenzo[*b*]thiophene hydrochloride with paraldehyde and dilute hydrochloric acid.⁵⁴⁵ 5-Amino-3-phenylbenzo-



⁵⁵⁵ E. I. du Pont de Nemours & Co., British Patent 695,164 (1953); *Chem. Abstr.* **49**, 755 (1955).

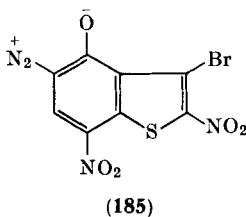
⁵⁵⁶ J. J. Lewis, M. Martin-Smith, T. C. Muir, S. N. Nanjappa, and S. T. Reid, *J. Med. Chem.* **6**, 711 (1963).

⁵⁵⁷ F. D'Alo, A. Masserini, and F. Bonacina, *Boll. Chim. Farm.* **103**, 709 (1964).

⁵⁵⁸ A. Ricci, N. P. Buu-Hoï, P. Jacquignon, and M. Dufour, *J. Heterocyclic Chem.* **2**, 300 (1965).

[*b*]thiophene undergoes the Ullmann-Fetvadjan reaction with 2-naphthol and paraformaldehyde to yield the acridine (184); related compounds are obtained when 2-naphthol is replaced by 1-naphthol or thioindoxyl.⁵⁵⁸

Bromination and nitration of 5-acetamidobenzo[*b*]thiophene⁴²² and its 2-carboxylic acid,⁴⁹⁷ and bromination of 5-aminobenzo[*b*]thiophene,⁴²² its 2-carboxylic acid,⁴⁹⁷ and its 3-bromo derivative,¹⁵² take place in the 4-position. 5-Amino-4-bromobenzo[*b*]thiophene is brominated in the 6-position, whereas 5-acetamido-4-bromobenzo[*b*]thiophene is brominated in the 3-position.¹⁵² Treatment of 5-acetamido-3-bromobenzo[*b*]thiophene with an excess of nitric acid in hot



acetic acid gives the *ortho*-diazooxide (185), the structure of which has been proved by X-ray crystallography.⁵⁵⁹ When the sulfur atom of 5-amino- or 5-acetamidobenzo[*b*]thiophene is oxidized to the 1,1-dioxide, electrophilic attack takes place preferentially in the 6-position.⁴²²

5. 6-Aminobenzo[*b*]thiophenes

Catalytic cyclodehydrogenation of 5-amino-2-ethylthiophenol affords 6-aminobenzo[*b*]thiophene.^{239, 241} 6-Acetamido-2,3-dibromo-,⁷⁷ 6-acetamido-2-bromo-3-methyl-,¹⁰² 6-acetamido-3-bromo-2-methyl-,¹⁰² and 6-acetamido-3-bromobenzo[*b*]thiophene¹⁰⁷ may be obtained from the corresponding 6-acetyl compound by means of the Schmidt reaction. In some cases the 6-acetamido compound is accompanied by a smaller amount of the amine sulfate.^{102, 107} 6-Aminobenzo[*b*]thiophene may be converted into 6-chloro- or 6-cyanobenzo[*b*]thiophene by means of the Sandmeyer reaction.²⁴¹

⁵⁵⁹ I. Brown, M. Martin-Smith, S. T. Reid, C. C. Scott, and G. A. Sim, *Chem. & Ind. (London)* 982 (1962).

TABLE X
 AMINO BENZO[*b*]THIOPHENES^a

Amine	Melting point (°C)	Yield (%)	Ref.
2-NH ₂	115-117	45, 80, 51	441, 112, 114
2-NH ₂ , 3-Me	Oil	78	113
2-NHAc, 3-Me	182.5-183	55, 50	481, 102
2,3-diNHAc	272-274	75	117
2-NHAc, 5,6-OCH ₂ O-	241	70	548
x-NHAc, 5,6-OCH ₂ O-	227-228	27	548
2-NHAc, 5-Br	238-239	74	76
2-NH ₂ (sulfate), 5-Br	250-255	82	76
2-NHPh	117-118	—	541
3-NH ₂	37-38	60	84
3-NHAc	169-171	89	117
3-NHAc, 5-Cl	202-204	80	117
3-NHAc, 5-Br	226-227	80, 70	117, 76
3-NH ₂ (sulfate), 5-Br ^b	235-240	74	76
3-NHAc, 7-Me	148.5-149.5	71	78
3-NHAc, 2-Me	186-186.5	51, 82	481, 102
3-NHAc, 2-(2-Naphthyl)	171	88	54
3-NHPh	88	90	541
3-NHC ₆ H ₄ -Me- <i>o</i>	54	63	554
3-NHC ₆ H ₄ -Me- <i>m</i>	Oil	—	554
3-NHC ₆ H ₄ -Me- <i>p</i>	52	—	554
3-NH ₂ , 2-NO ₂	218-218.5	—	412
3-NHPh, 2-NO ₂	210-211	100	412
3-NEt ₂ , 2-NO ₂	54	100	412
4-NH ₂	52-52.5	95, 24, 32	84, 105, 241
5-NH ₂	71	60, 95, 19	545, 488, 239
5-NH ₂ (sulfate)	270-272	87	497
5-NH ₂ , 3-Me	51-52	80	298, 331
5-NH ₂ , 3-Br	80-82	60	152
5-NH ₂ , 3-OH	208	—	494
5-NH ₂ , 3-Ph	59-60	—	333
5-NH ₂ , 3-CN	134.5-135	80	337
5-NH ₂ , 3-Ph, 2-CO ₂ H	220-221	—	185, 333
5,7-diNH ₂ , 3-Ph, 2-CO ₂ H	154	—	334
5,7-diNH ₂ , 3-Ph	132-133	—	334
5-NH ₂ , 2-CO ₂ H	279-280	85	497, 338
5-NH ₂ , 2-CO ₂ Et	92-94	—	555
5-NHAc, 2-CO ₂ Me	151	54	152
5-NH ₂ , 3,6-Me ₂ , 2-CO ₂ H	271	90	330
5-NH ₂ , 4,6-Br ₂	119	33	152

TABLE X—*continued*

Amine	Melting point (°C)	Yield (%)	Ref.
6-NH ₂	114–115	80	239, 241
6-NHAc, 3-Br	145–146	89	107
6-NHAc, 2-Br, 3-Me	196–197	63	102
6-NHAc, 3-Br, 2-Me	181.5–182	71	102
6-NHAc, 2,3-Br ₂	200–201	80	77
7-NH ₂	Oil	67	84
7-NH ₂ , 3-Ph, 5-NO ₂ , 2-CO ₂ H	305	—	334

^a Where an amine has been obtained from a reaction only as a derivative, details of the derivative are given.

^b Obtained by hydrolysis of the corresponding acetamido compound.

6. 7-Aminobenzo[b]thiophenes

7-Aminobenzo[b]thiophene is prepared from 7-hydroxybenzo[b]thiophene by means of the Bucherer reaction; it may be converted into 7-nitrobenzo[b]thiophene via the diazonium salt.⁸⁴ 5,7-Diamino-3-phenylbenzo[b]thiophene and its 2-carboxylic acid are prepared by reduction of the corresponding dinitro compound.³³⁴ Partial reduction of 5,7-dinitro-3-phenylbenzo[b]thiophene-2-carboxylic acid with ethanolic ammonium sulfide affords 7-amino-5-nitro-3-phenylbenzo[b]thiophene-2-carboxylic acid, the amino group of which may be replaced by hydrogen or iodine via the diazonium salt.³³⁴ 7-Amino-4-methoxybenzo[b]thiophene is mentioned in the patent literature.⁵⁶⁰

Aminobenzo[b]thiophenes are listed in Table X.

G. NITRILES

The methods used for preparing cyanobenzo[b]thiophenes are merely summarized in the present section; they are discussed in more detail elsewhere in this review. Cyanobenzo[b]thiophenes are most conveniently prepared by heating a halobenzo[b]thiophene with cuprous cyanide in a suitable solvent (Section VI, D, 2), or by means of a Sandmeyer reaction of the appropriate diazotized amine (Section VI, F, 4 and 5). Less commonly they are prepared from aldehydes or aldoximes, by methods described in Section VI, L, 1, or from carbox-

⁵⁶⁰ V. Georgian, U.S. Patent 2,858,314 (1958); *Chem. Abstr.* **53**, 10258 (1959).

amides by dehydration with phosphorus pentoxide⁵²¹ or acetic anhydride.¹¹⁴ 2-Cyano-3-methylbenzo[*b*]thiophene is a by-product of the reaction of 3-chloromethylbenzo[*b*]thiophene with potassium cyanide in dimethylsulfoxide.⁵²¹ The unsubstituted 2-cyano derivative is unknown.

A cyanobenzo[*b*]thiophene may be converted into the corresponding amidino compound by successive treatment with ammonium cyanate and acid.⁵⁶¹ 2-*p*-Cyanophenylbenzo[*b*]thiophene has been used to prepare the corresponding isocyanato compound, but no details have been given.³⁰² The hydrolysis of cyanobenzo[*b*]thiophenes is discussed in Section VI, M, 2; their reaction with Grignard reagents is discussed in Section VI, L, 3, *a*.

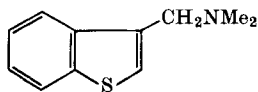
H. DERIVATIVES WITH NITROGEN IN A SIDE CHAIN

1. Nitro Compounds

The condensation of benzo[*b*]thiophene carboxaldehydes with nitroalkanes to give nitrovinylbenzo[*b*]thiophenes is discussed in Section VI, L, 1.

2. Amines

3-Aminomethylbenzo[*b*]thiophene⁵⁵⁶ and its 5-hydroxy derivative⁵⁶² may be prepared by a Gabriel synthesis from the corresponding



(186)

3-halomethylbenzo[*b*]thiophene. 3-Aminomethylbenzo[*b*]thiophene affords an *N,N*-dimethyl derivative (186) on alkylation with a mixture of aqueous formaldehyde and formic acid.⁵⁵⁶ This compound is the sulfur analog of gramine; it may also be prepared by treating 3-bromomethylbenzo[*b*]thiophene with dimethylamine.⁴⁸⁹ The intense interest in gramine as a biologically active compound has led to the synthesis of a large number of sulfur analogs, by treating a halomethylbenzo[*b*]thiophene with the appropriate amine,^{489, 492, 556, 563} by reducing the

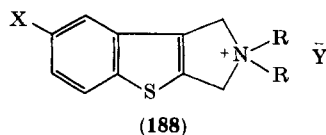
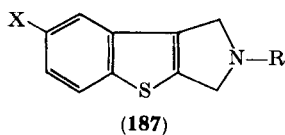
⁵⁶¹ O. Dann, Belgian Patent 659,379 (1965); *Chem. Abstr.* **64**, 3486 (1966).

⁵⁶² E. Campaigne and T. R. Bosin, *J. Med. Chem.* **11**, 178 (1968).

⁵⁶³ W. Voegtli, U.S. Patent 2,806,034 (1957); *Chem. Abstr.* **52**, 2931 (1958).

corresponding carboxamide with lithium aluminum hydride,^{337, 564} or by reduction of a Schiff's base with sodium borohydride.⁵⁶⁵

The course of the reactions of 2,3-di(bromomethyl)benzo[b]thiophenes with primary amines depends on the structure of the amine. They may react normally with 2 molar equivalents of the amine,⁴⁹² they may react with only 1 molar equivalent to give a cyclic tertiary



X = H, Cl, or Br

amine (187),^{492, 527} or they may give rise to mixtures of the two types of products.⁴⁹² 2,3-Di(bromomethyl)benzo[b]thiophenes react with secondary amines to give only cyclic quaternary ammonium salts (188).^{492, 527}

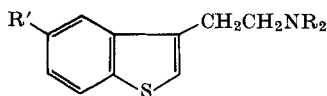
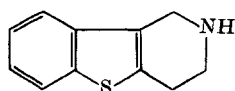
The sulfur analog of tryptamine (189a) may be prepared by electrolytic⁵⁶⁶ or lithium aluminum hydride^{531, 567} reduction of 3-cyanomethylbenzo[b]thiophene. Its 2-isomer may be prepared by a Gabriel synthesis from 2-(2-iodoethyl)benzo[b]thiophene; treatment of the hexamine salt from the latter compound with hydrochloric acid (Delépine reaction) does not give 2-(2-aminoethyl)benzo[b]thiophene, but affords 1,2,3,4-tetrahydrobenzothieno[3,2-c]pyridine (190).⁵²⁹ The biological activity of 5-hydroxytryptamine (serotonin) prompted the synthesis of its sulfur analog (189b). Reduction of the carboxamide (191) with lithium aluminum hydride, followed by either acidic hydrolysis or catalytic hydrogenolysis of the product, was unsuccessful,³³⁷ but Martin-Smith and co-workers³³⁷ prepared 189b in low yield by catalytic hydrogenation of 3-cyanomethyl-5-hydroxybenzo[b]thiophene, and Campaigne and co-workers³⁴³ have also made it in low yield by lithium aluminum hydride reduction of 5-benzoyloxy-3-(2-nitrovinyl)benzo[b]thiophene (192).

⁵⁶⁴ D. A. Shirley and M. D. Cameron, *J. Am. Chem. Soc.* **74**, 664 (1952).

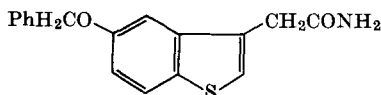
⁵⁶⁵ A. Hofmann and F. Troxler, Swiss Patent 442,353 (1968); *Chem. Abstr.* **69**, 43783 (1968).

⁵⁶⁶ H. Kotake and T. Sakan, *J. Inst. Polytech., Osaka City Univ.* **C2**, 25 (1951); *Chem. Abstr.* **46**, 6121 (1952).

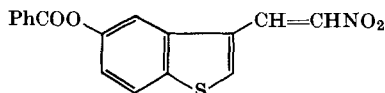
⁵⁶⁷ W. Herz, *J. Am. Chem. Soc.* **72**, 4999 (1950).

(189a) $R = R' = H$ (189b) $R = H, R' = OH$ 

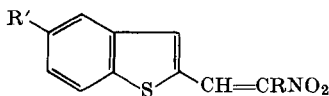
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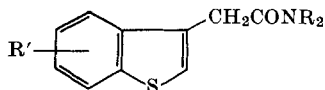
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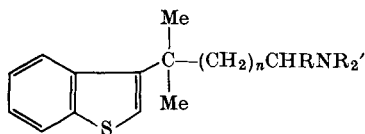


(193)



(194)

Reduction of the nitro compounds (**193**; $R = R' = H$, or $R = Me$, $R' = OH$) with lithium aluminum hydride affords the corresponding saturated amine.⁵⁵⁶ Similar reduction of carboxamides with the general formula (**194**) affords the corresponding amines^{143, 311, 313, 568, 569}; in the case of **194** ($R = H$, $R' = 6\text{-OMe}$), reduction with borane tetrahydrofuranate is more satisfactory.³¹²



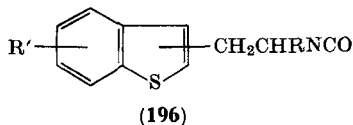
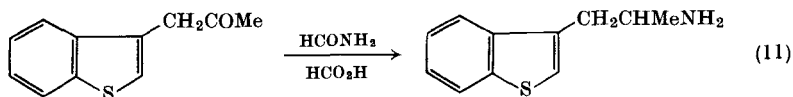
(195)

Cope and Burrows⁴¹⁴ have prepared a number of aminoalkylbenzo-*[b]*thiophenes with the general formula (**195**) by Friedel-Crafts reaction between benzo-*[b]*thiophene and various amino tertiary alcohols. On treatment with formamide in formic acid, (3-benzo-*[b]*-thienyl)acetone affords 3-(2-aminopropyl)benzo-*[b]*thiophene [Eq. (11)].⁵⁵⁷ Recent patents^{535, 570} describe how isocyanates with the

⁵⁵⁶ F. Sauter, L. Golser, and P. Stütz, *Monatsh. Chem.* **98**, 2089 (1967).

⁵⁶⁹ M. Martin-Smith and S. T. Reid, *J. Chem. Soc., C* 1897 (1967).

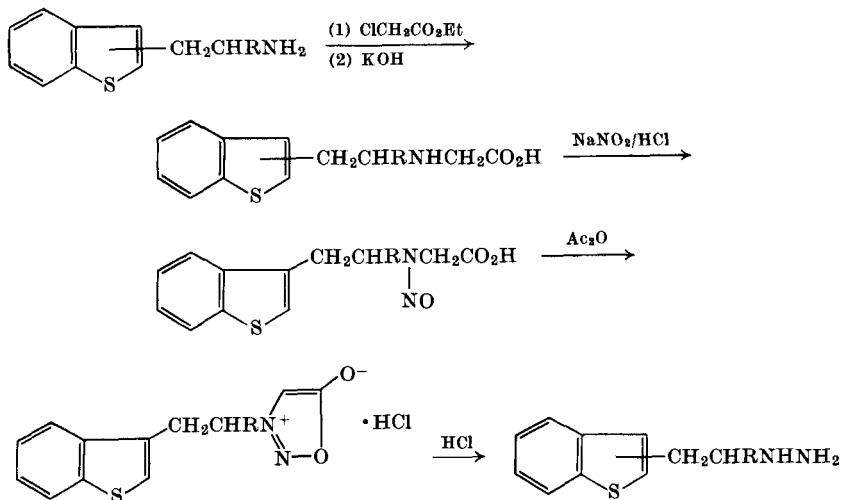
⁵⁷⁰ E. L. Anderson, U.S. Patent 3,070,606 (1962); Smith Kline and French Laboratories, British Patent 855,115 (1960); *Chem. Abstr.* **55**, 12423 (1961).



general formula (196) can be hydrolyzed to the corresponding aminoalkylbenzo[*b*]thiophene with hydrochloric acid, or reduced by lithium aluminum hydride to the corresponding *N*-methyl derivative; the products may be *N*-alkylated by a variety of procedures.

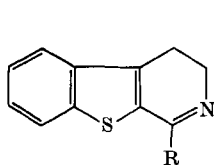
Several 2- and 3-(2-aminoalkyl)benzo[*b*]thiophenes have been converted into hydrazine derivatives by the reactions shown in Scheme 5.⁵³⁵

The *N*-acetyl and *N*-benzoyl derivatives of **189a** undergo a Bischler-Napieralski reaction with a mixture of phosphorus oxychloride and

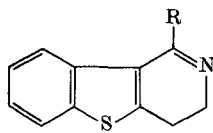


SCHEME 5

phosphorus pentoxide to give 1-methyl- or 1-phenyl-3,4-dihydrobenzothieno[2,3-*c*]pyridine (**197**; R = Me or Ph).⁵⁶⁷ The 7-ethoxy derivative of **197** (R = Me)⁵⁶⁹ and compounds (**198**; R = Me or Ph)⁵²⁹



(197)

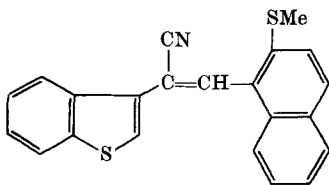


(198)

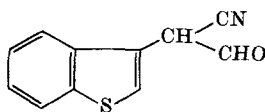
may be prepared similarly from the corresponding 2- or 3-(2-aminoethyl)benzo[*b*]thiophene. With formaldehyde **189a** affords 1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyridine.⁵⁶⁶

3. Nitriles

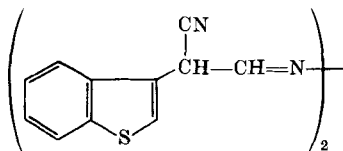
The preparation of cyanomethylbenzo[*b*]thiophenes by reaction of halomethylbenzo[*b*]thiophenes with alkali metal cyanides is discussed in Section VI, D, 4. Reduction of cyanomethylbenzo[*b*]thiophenes affords (2-aminoethyl)benzo[*b*]thiophenes (Section VI, H, 2), and they give the corresponding benzo[*b*]thienylacetic acid on alkaline hydrolysis (Section VI, M, 3).



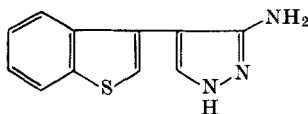
(199)



(200)



(201)



(202)

3-Cyanomethylbenzo[*b*]thiophene condenses with 2-methylthio-1-naphthaldehyde to give **199**,⁵⁷¹ and it affords **200** on formylation with ethyl formate and sodium methoxide.⁵²⁴ Compound **200** reacts with hydrazine under suitable conditions to give either **201** or 3-amino-4-(3-benzo[*b*]thienyl)pyrazole (**202**).⁵²⁴ With ethylene-

⁵⁷¹ N. P. Buï-Hoi, N. Hoán, and D. Lavit, *J. Chem. Soc.* 485 (1953).

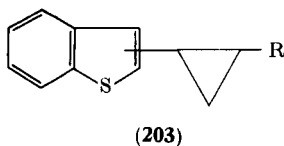
diamine mono-*p*-toluenesulfonate at 225°–230°, 3-cyanomethyl-2-methylbenzo[*b*]thiophene gives the imidazoline (2).^{525, 530}

4. Isocyanates

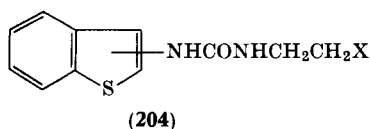
Three patents^{535, 570} describe the preparation of several isocyanates with the general formula (196), but few details of the compounds are given.

5. Miscellaneous Compounds

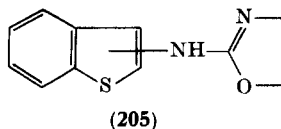
Amino ketones are discussed in Section VI, L, 3, c, and amino alcohols and benzo[*b*]thiophenes containing the 2-haloethylamine moiety are considered in Section VI, J.



2-(2- and 3-benzo[*b*]thienyl)cyclopropylamine (203; R = NH₂) may be prepared from the corresponding 2-(benzo[*b*]thienyl)cyclopropanecarboxylic acid by means of the Curtius reaction.⁴⁶⁶



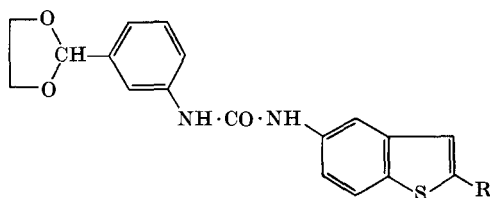
X = Cl, Br, or I



In two patents, Bloom⁵⁷² has described how 2-, 3-, and 4-benzo[*b*]thienylisocyanate may be converted by reaction with β -haloethylamines into the corresponding *N*-(benzo[*b*]thienyl)-*N'*- β -haloethylureas (204) which readily cyclize to 2-(benzo[*b*]thienylamino)-oxazolines (205) on being boiled in aqueous solution.

Ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate reacts with phosphene to give the corresponding isocyanate, which condenses with *m*-aminobenzaldehyde ethylene ketal to give the substituted urea (206a).⁵⁵⁵ With sodium methoxide and acetonitrile, 206a gives 206b.

⁵⁷² B. M. Bloom, U.S. Patent 2,992,232 (1961); *Chem. Abstr.* 55, 24792 (1961); U.S. Patent 2,870,160 (1959); *Chem. Abstr.* 53, 16153 (1959).

(206a) R = CO₂Et(206b) R = COCH₂CN

I. HYDROXYBENZO[*b*]THIOPHENES

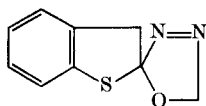
Apart from a single claim to the contrary, most workers have shown spectroscopically (Section III, B) that 2- and 3-hydroxybenzo[*b*]thiophene exist exclusively as their oxo tautomers. They are therefore more correctly called benzo[*b*]thiophen-2(3*H*)-one (*Chemical Abstracts* uses this terminology) or 2,3-dihydrobenzo[*b*]thiophen-2-one and benzo[*b*]thiophen-3(2*H*)-one or 2,3-dihydrobenzo[*b*]thiophen-3-one, respectively. To avoid confusion, especially for derivatives of these compounds for which little is known of their spectroscopic behavior, we shall use the simpler nomenclature, thiooxindole and thioindoxyl, respectively.

1. Thiooxindoles (2-Hydroxybenzo[*b*]thiophenes)

Thiooxindole (**15**) may be prepared by treating 2-benzo[*b*]thienyllithium with oxygen,^{112, 539, 541} by diazotization of 2-aminobenzo[*b*]thiophene followed by hydrolysis of the resulting diazonium salt,¹¹² by direct hydrolysis of 2-aminobenzo[*b*]thiophene with hydrochloric acid,^{84, 112} or by treatment of either ethyl 2-acetamidobenzo[*b*]thiophene-3-carboxylate^{114, 441} or ethyl 2-aminobenzo[*b*]thiophene-3-carboxylate⁴⁴¹ with sodium hydroxide. It is formed in low yield (15%), together with benzo[*b*]thiophene (65%) when 3-bromobenzo[*b*]thiophene is treated with ethanolic potassium hydroxide (Section V, C).⁴⁰⁵ *o*-Mercaptophenylacetic acid, obtained by heating the 3-hydrazone of benzo[*b*]thiophene-2,3-quinone with potassium hydroxide, readily cyclizes to thiooxindole on treatment with steam and hydrochloric acid.⁵⁷³ 6-(Ethoxy)thiooxindole may be prepared similarly.⁵⁷³ The imine (**14**) may be hydrolyzed with acid to the corresponding thiooxindole derivative (**16**).¹¹³

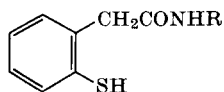
⁵⁷³ R. H. Glauert and F. G. Mann, *J. Chem. Soc.* 2127 (1952); British Patent 684,187 (1952); *Chem. Abstr.* **47**, 6290 (1953).

It has been suggested that the oxo and enol tautomers of thiooxindole^{573, 574} and its 6-ethoxy derivative⁵⁷³ may each be isolated. However, it has recently been shown spectroscopically (Section III, B) that thiooxindole exists solely in the oxo form, in the solid phase and in solution.^{84, 112, 113}

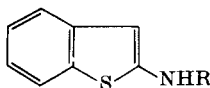


(207)

Diazomethane reacts with thiooxindole to give the spirooxadiazole (207).⁴⁰⁰ The reactivity of thiooxindole toward amines differs markedly from that of thioindoxyl (Section VI, I, 2).^{539, 541} In most



(208)



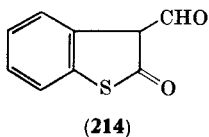
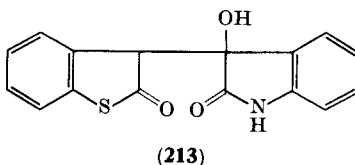
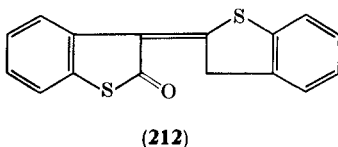
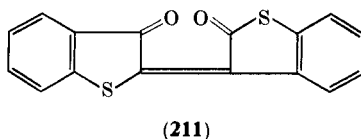
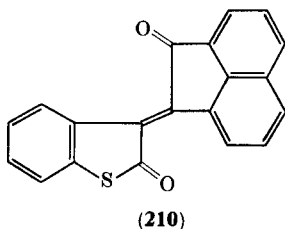
(209)

cases no reaction occurs and, when reaction does occur (e.g., with aniline and benzylamine), an intermediate amide (208) is formed which proceeds to the expected product (209) only in the case of aniline. Thiooxindole condenses with 1,2-dicarbonyl compounds with some difficulty. With acenaphthenequinone it affords **210**, and with benzo[*b*]thiophene-2,3-quinone a mixture of products is obtained, from which thioindirubin (**211**) has been isolated.⁵⁷⁵ In the presence of sodium hydride, thiooxindole undergoes self-condensation to give a product for which structure **212** has been proposed.⁵⁷⁵ With isatin, the addition compound (**213**) is formed.⁵⁷⁵

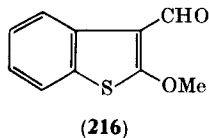
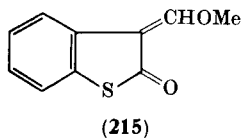
2-Methoxybenzo[*b*]thiophene may be prepared by treating 2-bromobenzo[*b*]thiophene with sodium methoxide; it is metallated by *n*-butyllithium, and undergoes electrophilic substitution in the 3-position.¹⁸³

⁵⁷⁴ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 66. Wiley (Interscience), New York, 1954.

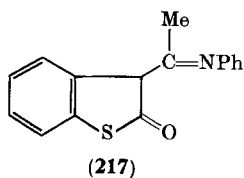
⁵⁷⁵ J. N. Chatterjea and A. K. Mitra, *J. Indian Chem. Soc.* **36**, 315 (1959).



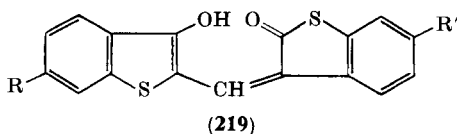
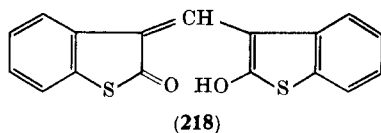
Thioxindole-3-carboxaldehyde (**214**) may be prepared by three methods; the most convenient involves condensation of thioxindole with diphenylformamidine to give the anil, which affords the aldehyde in high yield on alkaline hydrolysis.⁵⁷³ 6-(Ethoxy)thioxindole-3-carboxaldehyde may be prepared similarly.⁵⁷⁵ Thioxindole-3-carboxaldehyde may also be prepared (in low yield) from thioxindole by the Gattermann reaction⁵⁷³ and by alkaline hydrolysis of the condensation product formed between indoxyl and benzo[*b*]-thiophene-2,3-quinone.⁵⁷³ The latter procedure may also be used to prepare 6-ethoxy- and 6-chloro-4-(methyl)thioxindole-3-carboxaldehyde (see also Section VI, I, 2).⁵⁷³



Thioxindole-3-carboxaldehyde reacts with diazomethane to give a mixture of 3-acetyl-2-methoxybenzo[*b*]thiophene and a compound for which two possible structures (**215** or **216**) have been proposed.⁵⁷³ The aldehyde is hydrolyzed by acids to thioxindole.⁵⁷⁵



3-(Acetyl)thiooxindole may be prepared by fusing together thiooxindole and *N,N'*-diphenylacetamidine to give the anil (217), which affords the acetyl compound on alkaline hydrolysis.⁵⁷³ Acetylation and benzylation of thiooxindole are possible by using mixtures of acetic anhydride and sodium acetate or benzoic anhydride and sodium benzoate, respectively.⁵⁷⁵



Thiooxindole condenses with its 3-formyl derivative (214) in the presence of triethylamine to give the oxonol (218), and with thioindoxyl-2-carboxaldehyde in the presence of acid or base to give the oxonol (219; R = R' = H).⁵⁷⁶ Oxonols (219; R = Et, R' = H, or R = H, R' = Et) may be prepared similarly.⁵⁷⁶

Several merocyanine dyes have been prepared from thiooxindole.⁵⁷⁷⁻⁵⁸⁰

2. Thioindoxyls (3-Hydroxybenzo[*b*]thiophenes)

Thioindoxyls are usually prepared by ring closure (Section IV, D). 2-(Phenyl)thioindoxyl is obtained when 2,2'-diphenylthioindigo

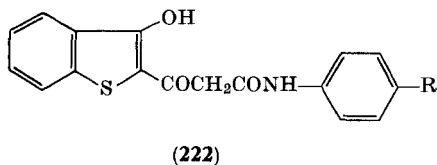
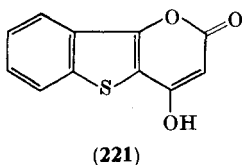
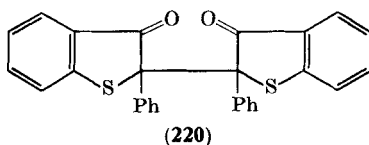
⁵⁷⁶ R. H. Glauert, F. G. Mann, and A. J. Wilkinson, *J. Chem. Soc.* 30 (1955).

⁵⁷⁷ R. H. Glauert and F. G. Mann, *J. Chem. Soc.* 2135 (1952).

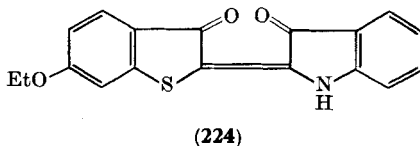
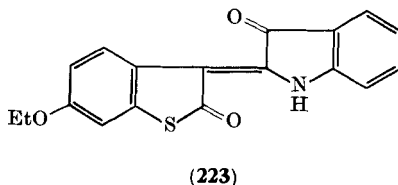
⁵⁷⁸ R. H. Glauert and F. G. Mann, *J. Chem. Soc.* 5012 (1952).

⁵⁷⁹ R. H. Glauert, F. G. Mann, and A. J. Wilkinson, *J. Chem. Soc.* 28 (1955).

⁵⁸⁰ R. H. Glauert and F. G. Mann, *J. Chem. Soc.* 2537 (1955).



white (220) is treated with phenylmagnesium bromide.⁵⁸¹ Various 4-hydroxy-2-oxopyrano[3,2-*b*]benzo[*b*]thiophenes undergo ring opening on treatment with base to give thioindoxyl derivatives,^{582, 583} e.g., compound **221** reacts with aniline or *p*-toluidine to give compound **222** (R = H or Me).⁵⁸²



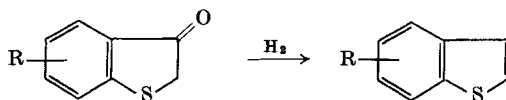
6-Ethoxybenzo[*b*]thiophene-2,3-quinone condenses with indoxyl to give a mixture of **223** and **224**.⁵⁷³ When this mixture is heated with aqueous potassium hydroxide, only **223** is hydrolyzed to give 6-(ethoxy)thiooxindole-3-carboxaldehyde and anthranilic acid. However, if the residue (containing **224**) is treated with hot ethanolic potassium hydroxide, **224** is hydrolyzed to give 6-(ethoxy)thioindoxyl-2-carboxaldehyde and anthranilic acid. Other substituted

⁵⁸¹ A. Mustafa and A. M. Islam, *J. Chem. Soc.* 1616 (1951).

⁵⁸² A. Mustafa, W. Asker, O. H. Hishmat, M. I. Ali, A.-K. E. Mansour, N. M. Abed, K. M. A. Khalil, and S. M. Samy, *Tetrahedron* **21**, 849 (1965).

⁵⁸³ E. Ziegler and F. Eichenseer, *Monatsh. Chem.* **97**, 391 (1966).

TABLE XI
 BENZO[*b*]THIOPHENES BY REDUCTION OF THIOINDOXYLS
 (3-HYDROXYBENZO[*b*]THIOPHENES)



Substituents	Melting point and/or boiling point (°C)	Yield (%)	Method ^a	Ref.
None	31–31.5	86, 80	b	222, 432
6-Me	?	?	a	585
7-Me	?	ca. 50	a	585
2-Et	Oil	68	b	222
5-Br	47	90	a	315
6-Br	56	Moderate	a	315
6-Cl	42–43	?	a	241
7-Cl	?	ca. 50	a	585
7-Me, 5-Br	(100–101/3 mm)	?	a	106
4,5,6,7-F ₄ , 2-CO ₂ Et	35–40 ^b	low	a	109
6-OMe	(80/0.1 mm)	?	a	42
6-OEt	41–42	81, 69	b, c	424
7-CO ₂ H	172	55	a	315

^a For a discussion see text.

^b Product was 4,5,6,7-tetrafluorobenzo[*b*]thiophene.

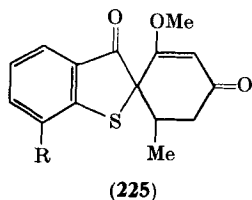
thiooxindole-3-carboxaldehydes and thioindoxyl-2-carboxaldehydes may be prepared similarly.⁵⁷³ Thioindoxyl-2-carboxaldehyde and its 6-ethoxy and 6-chloro-4-methyl derivatives may also be prepared from the corresponding thioindoxyls by the Gattermann reaction.⁵⁷³ Thioindoxyl reacts with *N,N'*-diphenylacetamidine to give the anil of 2-(acetyl)thioindoxyl.⁵⁷³

Thioindoxyls are readily oxidized to thioindigo dyes.⁵⁸⁴ They may be reduced to benzo[*b*]thiophenes (Table XI) with zinc (Clemmensen reduction) or tin and acid (method a) (use of mossy zinc is preferred for the reduction of halothioindoxyls and also minimizes reduction of the thiophene ring),³¹⁵ sodium borohydride (method b),^{222, 424, 432} or

⁵⁸⁴ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 84. Wiley (Interscience), New York, 1954.

lithium aluminum hydride (method c).⁴²⁴ Modified Wolff-Kishner^{281, 426} or Clemmensen¹⁸² reduction of thioindoxyl and its alkyl derivatives affords the corresponding 2,3-dihydrobenzo[*b*]thiophenes (Section VI, B, 1). Metal-acid reduction of halothioindoxyls affords the corresponding halobenzo[*b*]thiophene in rather poor yield,^{106, 241, 315, 585} but the method is of some preparative use in the case of the otherwise rather inaccessible 6-halobenzo[*b*]thiophenes.^{241, 315} 4,5,6,7-Tetrafluorobenzo[*b*]thiophene is formed in very low yield by the simultaneous hydrolysis, reduction, and decarboxylation of ethyl 4,5,6,7-tetrafluorothioindoxyl-2-carboxylate with zinc dust in a mixture of water, acetic acid, and sulfuric acid.¹⁰⁹ Use of sodium borohydride prevents further reduction of the thiophene ring; 2,3-dihydrobenzo[*b*]thiophene-3-ols are formed as isolable intermediates in this case (Section VI, B, 1). Electrolytic reduction of thioindoxyl affords 2,3-dihydrobenzo[*b*]thiophene-3-ol.⁵⁸⁶

Thioindoxyl and its 6-ethoxy derivative undergo the Reformatsky reaction with ethyl bromoacetate to give the corresponding 3-benzo[*b*]thienylacetic acid, on alkaline hydrolysis of the reaction mixture.⁵⁶⁹



Thioindoxyl and its 7-chloro derivative undergo a Michael reaction with methoxyethynyl prop-1-enyl ketone to give low yields of the (*d,d*)-racemic spirans (**225**; R = H or Cl), which are analogs of griseofulvin.¹⁴⁷

Successive treatment of thioindoxyl with sodium methoxide and methyl chloroacetate affords methyl 3-benzo[*b*]thienyloxyacetate.⁵⁸⁷

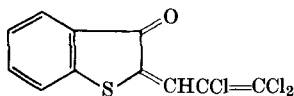
Thioindoxyl condenses with various primary aliphatic and primary and secondary aromatic amines to give 3-aminobenzo[*b*]thiophenes^{539, 541, 553, 554}; condensation with secondary aliphatic amines

⁵⁸⁵ A. Mustafa and S. M. A. D. Zayed, *J. Am. Chem. Soc.* **78**, 6174 (1956).

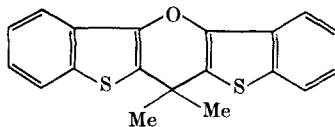
⁵⁸⁶ N. Kucharczyk, M. Adamovský, V. Horák, and P. Zuman, *J. Electroanal. Chem.* **10**, 503 (1965).

⁵⁸⁷ F. F. Blicke, U.S. Patent 2,645,572 (1953); *Chem. Abstr.* **47**, 10798 (1953).

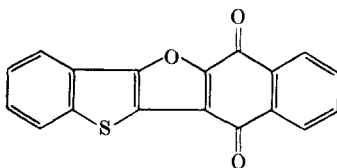
proceeds either in poor yields or not at all.^{539, 541} It undergoes the Ullmann-Fetvadjian reaction with a number of primary aromatic amines (see also Section VI, F, 4).^{553, 558} Fischer cyclization of the



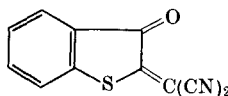
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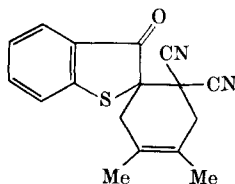
(227)



(228)



(229)



(230)

arylhydrazones of thioindoxyls affords 10*H*-[1]benzothieno[3,2-*b*]-indoles.^{319, 554, 588, 589} The 2-methylene group of thioindoxyls condenses with aromatic aldehydes to give 2-arylidene-2,3-dihydrobenzo[*b*]thiophen-3-ones (see also Sections III, D and VI, C, 3),^{42, 222, 286, 432, 590-593} with *p*-nitroso-*N,N*-dimethylaniline to give anils of benzo[*b*]thiophene-2,3-quinones (Section VI, K), and with a variety of

⁵⁸⁸ L. H. Werner, U.S. Patent 3,024,248 (1962); *Chem. Abstr.* **57**, 8580 (1962); Ciba Ltd., British Patent 830,223 (1960); *Chem. Abstr.* **54**, 18550 (1960).

⁵⁸⁹ N. P. Buu-Hoi and G. Saint-Ruf, *Israel J. Chem.* **1**, 369 (1963).

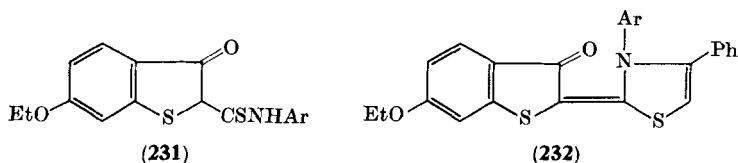
⁵⁹⁰ V. A. Izmail'skii and M. A. Mostoslavskii, *Zh. Obshch. Khim.* **31**, 3839 (1961); *Chem. Abstr.* **57**, 9775 (1962).

⁵⁹¹ A. K. Sinha, *J. Indian Chem. Soc.* **39**, 165 (1962).

⁵⁹² S. K. Guha, J. N. Chatterjea, and A. K. Sinha, *J. Indian Chem. Soc.* **32**, 777 (1955).

⁵⁹³ S. K. Guha, J. N. Chatterjea, and A. K. Mitra, *Chem. Ber.* **94**, 3297 (1961).

diazonium salts to give azo dyes⁵⁹⁴⁻⁶⁰² or 2-phenylhydrazono-2,3-dihydrobenzo[*b*]thiophen-3-ones.⁶⁰² Condensation of thioindoxyl with trichloroacetaldehyde,⁶⁰³ acetone,⁶⁰⁴ 2,3-dichloro-1,4-naphthoquinone,⁵⁵³ or tetracyanoethylene⁶⁰⁵ gives **226**, **227**, **228**, or **229**, respectively. The structure of **228** has not been proved conclusively. Compound **229** undergoes a Diels-Alder reaction with 2,3-dimethylbutadiene to give **230**.⁶⁰⁵ Condensation of 6-(ethoxy)thioindoxyl with arylisothiocyanates in the presence of sodium gives compounds with



the general formula (231), which afford thiazolines (232) on treatment with phenacyl bromide.⁶⁰²

Treatment of thioindoxyl and its 5-methyl derivative with *O,O*-diethyl chlorothiophosphate in the presence of base affords the corresponding *O,O*-diethyl-*O*-(3-benzo[*b*]thienyl)thiophosphate.⁶⁰⁶ *O,O*-

⁵⁹⁴ H. Baumann, German Patent 1,003,374 (1957); *Chem. Abstr.* **54**, 3970 (1960).

⁵⁹⁵ R. F. M. Sureau, G. R. H. Mingasson, G. H. V. Kremer, and J. L. A. Rollet, French Patent 1,160,503 (1958); *Chem. Abstr.* **55**, 19256 (1961).

⁵⁹⁶ R. F. M. Sureau, G. R. H. Mingasson, J. L. A. Rollet, G. H. V. Kremer, and R. Pernot, French Patent addn. 69,946 (1959); *Chem. Abstr.* **55**, 10902 (1961); French Patent 1,129,702 (1957); *Chem. Abstr.* **54**, 2758 (1960).

⁵⁹⁷ J. M. Straley and R. R. Giles, U.S. Patent 2,868,775 (1959); *Chem. Abstr.* **53**, 7609 (1959).

⁵⁹⁸ Badische Anilin- & Soda-Fabrik A.-G., British Patent 824,300 (1959); *Chem. Abstr.* **54**, 8093 (1960).

⁵⁹⁹ A.C.N.A. Aziende Colori Nazionali Affini, S.p.A., British Patent 961,213 (1964); *Chem. Abstr.* **61**, 9613 (1964).

⁶⁰⁰ P. C. Dutta, A. Kumar, S. Gupta, B. P. Bose, and S. K. Roy, *J. Indian Chem. Soc.* **37**, 50 (1960).

⁶⁰¹ M. Lipp and S. M. Abd Elrahman Omran, *Melliand Textilber.* **42**, 792 (1961).

⁶⁰² M. O. Lozinskii, S. N. Sanova, and P. S. Pel'kis, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* **461** (1967); *Chem. Abstr.* **68**, 29505 (1968).

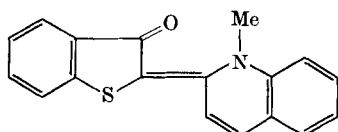
⁶⁰³ A. Roedig and S. Schödel, *Chem. Ber.* **91**, 320 (1958).

⁶⁰⁴ N. Kucharczyk, V. Horák, and M. Semonský, *Collection Czech. Chem. Commun.* **32**, 2377 (1967).

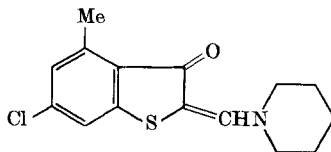
⁶⁰⁵ J. W. Van Dyke and H. R. Snyder, *J. Org. Chem.* **27**, 3888 (1962).

⁶⁰⁶ T. Harukawa and T. Ishikawa, Japanese Patent 10,508 (1960); *Chem. Abstr.* **55**, 9441 (1961).

Diethyl-*O*-(6-methoxy-3-benzo[*b*]thienyl)phosphorothioate and a number of related compounds may be prepared similarly.⁶⁰⁷ These compounds exhibit pesticidal activity.

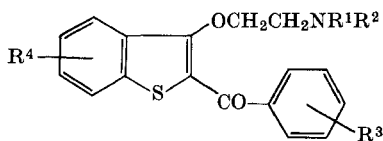


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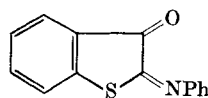


(234)

2-(Acetyl)thioindoxyl condenses with *o*-aminobenzaldehyde in the presence of base to give **233**,⁶⁰⁸ and 6-chloro-4-(methyl)thioindoxyl-2-carboxaldehyde condenses with piperidine to give **234**.⁵⁷⁷



(235)



(236)

2-(Aroyl)thioindoxyls condense with dialkylaminoethyl chlorides in the presence of base, to give compounds with the general formula **(235)**.²⁷²

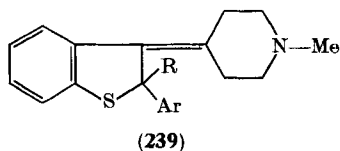
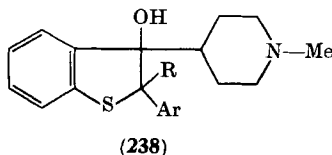
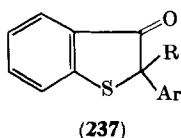
The anil **(236)** reacts with compounds of the type RCH_2R' ($R = R' = \text{COMe}$; $R = R' = \text{CO}_2\text{Et}$; $R = R' = \text{CN}$; $R = \text{COMe}$, $R' = \text{CO}_2\text{Et}$; or $R = \text{CN}$, $R' = \text{CO}_2\text{Et}$) in the presence of acetic anhydride, to give thioindogenides with the general formula **(29)** (see also Section III, D).²²⁷

2-(Aryl)thioindoxyls undergo both *C*- (in the 2-position) and *O*-alkylation in the presence of potassium *tert*-butoxide.⁶⁰⁹ The *C*-alkylated products **(237)** react with *N*-methylpiperidine-4-magnesium chloride to give compounds **(238)** (as mixtures of α - and β -racemates), which lose water on treatment with hydrogen bromide to give **239**.

⁶⁰⁷ K. J. Schmidt, German Patent 1,230,433 (1966); *Chem. Abstr.* **66**, 76154 (1967).

⁶⁰⁸ W. Jenny, *Helv. Chim. Acta* **34**, 539 (1951).

⁶⁰⁹ E. Merck A.-G., Netherlands Patent Appl. 6,413,199 (1965); *Chem. Abstr.* **63**, 18038 (1965).



3-Methoxybenzo[*b*]thiophene may be prepared by treating 3-bromobenzo[*b*]thiophene with sodium methoxide¹⁸³; it is metallated by *n*-butyllithium, and undergoes electrophilic substitution in the 2-position.^{93, 183} Vilsmeier-Haack formylation at a temperature not exceeding 45° gives the 2-formyl derivative^{93, 183} but, at 95°, displacement of the methoxyl group by chlorine occurs to give 3-chlorobenzo[*b*]thiophene-2-carboxaldehyde in good yield.⁹³ With dichlorocarbene, 3-methoxybenzo[*b*]thiophene undergoes ring expansion to give 3-chlorothiochromone.⁴⁰⁰

3. 4-Hydroxybenzo[*b*]thiophenes

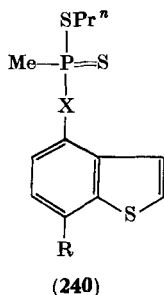
4-Hydroxybenzo[*b*]thiophene has been isolated from coal tar.⁴² It may be prepared by dehydrogenation of 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one (Section VI, B, 4), and from 4-aminobenzo[*b*]thiophene by standard procedures.⁴²²

Unlike thioindoxyl (Section VI, I, 2), 4-hydroxybenzo[*b*]thiophene will not condense with aniline, nor will it undergo a Ullmann-Fetvadjian reaction with 1-naphthylamine.⁵⁵⁴

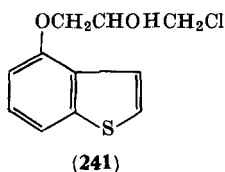
4-Benzo[*b*]thienyl *N*-methylcarbamate (tradename Mobam), and a number of other benzo[*b*]thienyl carbamates possessing insecticidal activity, have been prepared from the corresponding hydroxy compounds by means of standard reactions.^{610, 611} Compounds **240** (X = O,

⁶¹⁰ J. R. Kilsheimer and H. A. Kaufman, U.S. Patent 3,288,808 (1966); *Chem. Abstr.* **66**, 75904 (1967); Socony Mobil Oil Co., Inc., Belgian Patent 638,684 (1964); *Chem. Abstr.* **62**, 7729 (1965); Netherlands Patent Appl. 6,402,271 (1965); *Chem. Abstr.* **64**, 8137 (1966); U.S. Patent 3,288,673 (1966); *Chem. Abstr.* **66**, 104900 (1967).

⁶¹¹ A. J. Epstein, D. R. Gaskill, and C. A. Lucchesi, *Anal. Chem.* **39**, 721 (1967).



R = H, Me, NO₂, or SMe) are also reported to exhibit pesticidal activity.⁶¹² They may be prepared by treating a 4-hydroxybenzo[*b*]thiophene with *S*-*n*-propylmethylphosphonochloridothioate in the presence of triethylamine.



4-Hydroxybenzo[*b*]thiophene reacts with epichlorohydrin in the presence of piperidine to give 4-(3-chloro-2-hydroxypropoxy)benzo[*b*]thiophene (241), or in the presence of sodium hydroxide to give the corresponding epoxide.⁶¹³

4-Methoxybenzo[*b*]thiophene undergoes Friedel-Crafts acylation in the 7-position; if this position is blocked, then substitution occurs exclusively in the 2-position.⁶¹⁴ It undergoes Vilsmeier-Haack formylation to give its 7-formyl derivative.⁹³

4. 5-Hydroxybenzo[*b*]thiophenes

5-Hydroxy-,^{337, 342, 497} 5-methoxy-,³⁴¹ and 5-hydroxy-3-methylbenzo[*b*]thiophene³⁴³ are conveniently prepared by decarboxylation

⁶¹² Mobil Oil Corp., British Patent 1,097,634 (1968); *Chem. Abstr.* **69**, 10353 (1968).

⁶¹³ R. W. Turner, British Patent 1,089,769 (1967); Imperial Chemical Industries Ltd., Netherlands Patent Appl. 6,608,718 (1967); *Chem. Abstr.* **68**, 29586 (1968).

⁶¹⁴ M.-L. Desvoye, P. Demerseman, J.-P. Lechartier, C. Pène, A. Cheutin, and R. Royer, *Bull. Soc. Chim. France* 1473 (1965).

of the corresponding 2-carboxylic acid. 5-Methoxy- and 5-ethoxybenzo[*b*]thiophene may be prepared by cyclization of (*p*-methoxy- or *p*-ethoxyphenylthio)acetaldehyde dimethyl acetal (Section IV, B). 5-Methoxybenzo[*b*]thiophenes are readily demethylated with pyridine hydrochloride.⁶¹⁵ The 3- and 4-bromo,⁴²² 3-methyl,⁵⁵⁸ and 2-carboxy^{337, 497} derivatives of 5-hydroxybenzo[*b*]thiophene are made from the corresponding amines by standard procedures.

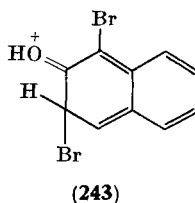
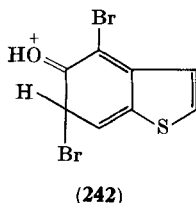
O-Sulfonylation (MeSO_2Cl or $\text{PhCH}_2\text{SO}_2\text{Cl}/\text{C}_5\text{H}_5\text{N}$) of 5-hydroxybenzo[*b*]thiophene gives 5-methane- or 5-benzylsulfonyloxybenzo[*b*]thiophene, respectively,³³⁷ and with epichlorohydrin it affords 5-(3-chloro-2-hydroxypropoxy)benzo[*b*]thiophene.⁶¹³ Potential pesticides, analogous to those described in Section VI, I, 3, have been prepared from 5-hydroxybenzo[*b*]thiophene.^{610, 612}

5-Acetoxybenzo[*b*]thiophene undergoes a Fries rearrangement to give 4-acetyl-5-hydroxybenzo[*b*]thiophene.³³⁸ The allyl ether of 5-hydroxybenzo[*b*]thiophene resembles that of phenol, rather than that of 2-naphthol, in its ability to undergo two successive Claisen rearrangements.⁴²² Thus, heating 5-allyloxybenzo[*b*]thiophene in dimethylaniline affords a product assumed to be 4-allyl-5-hydroxybenzo[*b*]thiophene. This can be converted into 4-allyl-5-allyloxybenzo[*b*]thiophene, which rearranges similarly to give a product assumed to be 4,6-diallyl-5-hydroxybenzo[*b*]thiophene. No satisfactory proof of the structures of these products has been given.

Electrophilic substitution reactions of 5-hydroxybenzo[*b*]thiophene have been investigated in some detail. The 4-position is the most reactive toward nitration,¹⁵² nitrosation,⁴⁹⁷ bromination,⁴²² and formylation (Duff procedure).³³⁸ Dibromination in the presence of acetate ion affords 4,6-dibromo-5-hydroxybenzo[*b*]thiophene,^{421, 422, 497} and not the 3,4-dibromo derivative, as previously believed.⁵⁴² Dichlorination similarly affords the 4,6-dichloro derivative,⁴²¹ and not 4,4-dichloro-4,5-dihydrobenzo[*b*]thiophen-5-one, as reported earlier by Fries *et al.*⁵⁴² An interesting comparison can be made between the behavior of 5-hydroxybenzo[*b*]thiophene and 2-naphthol in electrophilic substitution reactions. It is clear that both positions *ortho* to the hydroxyl group in 5-hydroxybenzo[*b*]thiophene are attacked, in contrast to 2-naphthol, where only the 1-position is attacked even in the presence of an excess of the reagent. Disubstitu-

⁶¹⁵ P. Demerseman, A.-M. Laval-Jeantet, J.-P. Lechartier, A. Cheutin, and R. Royer, *Compt. Rend.* **257**, 3002 (1963).

tion occurs fairly readily in the case of 5-hydroxybenzo[*b*]thiophene, but not in the case of 2-naphthol. This difference in behavior has been



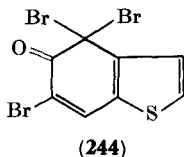
attributed to the relative ease of formation of a transition state of type **242** compared to that of type **243**.^{421, 422} This is claimed to be a manifestation of the lower resonance energy of a thiophene ring compared to that of a benzene ring.

Substitution in the 4-position is also favored by the presence of an amino or acetamido group at the 5-position (Section VI, F, 4). An acetoxy, benzoyloxy, methanesulfonyloxy, or benzyulsulfonyloxy group in the 5-position is not sufficient to activate the benzenoid ring toward attack in the 4-position; instead, electrophilic substitution occurs in the 3-position.^{337, 422}

5-Hydroxybenzo[*b*]thiophene-2-carboxylic acid is nitrated¹⁵² and nitrosated⁴⁹⁷ in the 4-position. Dibromination in the presence of acetate ion affords the 4,6-dibromo derivative.⁴²¹ Likewise, 3-bromo-5-hydroxybenzo[*b*]thiophene is nitrated in the 4-position; dinitration affords a product of unknown structure.¹⁵²

Nitration of 4-bromo-5-hydroxybenzo[*b*]thiophene occurs in the 6-position,¹⁵² and not in the 3-position as previously reported.⁵⁴² In contrast, 4-bromo-5-methoxybenzo[*b*]thiophene is brominated in the 3-position.¹⁵²

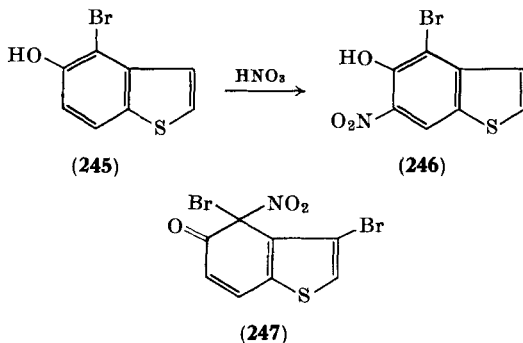
Further bromination of 4,6-dibromo-5-hydroxybenzo[*b*]thiophene affords either of two products, depending on the presence or absence of acetate ion. In the absence of acetate ion, bromination is slow, and 3,4,6-tribromo-5-hydroxybenzo[*b*]thiophene is obtained.⁴²¹ It is identical to the product of bromination of 3,4-dibromo-5-hydroxybenzo[*b*]thiophene in the presence of acetate ion. In the presence of acetate ion, bromination of 4,6-dibromo-5-hydroxybenzo[*b*]thiophene is rapid, and 4,4,6-tribromo-4,5-dihydrobenzo[*b*]thiophen-5-one (**244**) is obtained. The latter compound is converted into starting material on treatment with sodium hydrosulfite, and into a mixture of 4,6-



dibromo-5-hydroxybenzo[*b*]thiophene and 3,4,6-tribromobenzo[*b*]thiophene with hydrobromic acid in acetic acid.⁴²¹

Further bromination of 3,4,6-tribromo-5-hydroxybenzo[*b*]thiophene affords the 2,3,4,6-tetrabromo derivative in the absence of acetate ion, and 3,4,4,6-tetrabromo-4,5-dihydrobenzo[*b*]thiophen-5-one in the presence of acetate ion.⁴²¹ On treatment of 3,4-dibromo-, 4,6-dibromo-, 3,4,6-tribromo-, or 2,3,4,6-tetrabromo-5-hydroxybenzo[*b*]thiophene with nitric acid in acetic acid, the corresponding unstable orange crystalline 4-bromo-4-nitro-4,5-dihydrobenzo[*b*]thiophen-5-one is obtained.^{152, 421} Hence, once both positions *ortho* to the hydroxyl group in 5-hydroxybenzo[*b*]thiophene are occupied by bromine, the properties of these compounds are analogous to the properties of 1-bromo-2-naphthol which, on bromination in acetic acid in the presence of acetate ion, affords 1,1-dibromo-1,2-dihydronaphthalen-2-one whereas, in its absence, it affords 1,6-dibromo-2-naphthol.⁶¹⁶ The behavior of 1-bromo-2-naphthol and its derivatives on nitration is similar to that of 4,6-dibromo-5-hydroxybenzo[*b*]thiophene and its derivatives.^{152, 616}

The course of nitration of 4-bromo-5-hydroxybenzo[*b*]thiophene (245 → 246) is of interest; under the same experimental conditions 3,4-dibromo-5-hydroxybenzo[*b*]thiophene affords the keto compound



⁶¹⁶ Martin-Smith and Gates,⁴²¹ and references cited therein.

(**247**).¹⁵² Formation of **247** may be favored by steric factors, as the 3- and 4-positions of benzo[*b*]thiophene are analogous to the *peri* positions of naphthalene. Removal of the 4-substituent from the plane of the ring would be expected to relieve steric strain.

Like thioindoxyl (Section VI, I, 2) and 2-naphthol, but unlike thiooxindole (Section VI, I, 1) and 4-hydroxybenzo[*b*]thiophene (Section VI, I, 3), 5-hydroxybenzo[*b*]thiophene condenses readily with aromatic amines.⁵⁵⁸ It undergoes a normal Ullmann-Fetvadjan reaction with 1-naphthylamine to give 1-methylthieno[3,2-*a*]benz[*h*]acridine, but with 2-naphthylamine an inseparable mixture of 1-methylthieno[3,2-*a*]benz[*j*]acridine and dibenz[*a,j*]acridine is obtained.⁵⁵⁸

5. 6-Hydroxybenzo[*b*]thiophenes

6-Hydroxybenzo[*b*]thiophene has been isolated from coal tar.⁴² It may be prepared from 6-aminobenzo[*b*]thiophene by standard procedures.²⁴¹ 6-Methoxybenzo[*b*]thiophene may be prepared by decarboxylation of the corresponding 2-carboxylic acid,³⁴¹ and 6-ethoxybenzo[*b*]thiophene is obtained by reduction of 6-(ethoxy)-thioindoxyl (Section VI, I, 2). 6-Methoxy-5-methylbenzo[*b*]thiophene is obtained by cyclization of (3-methoxy-4-methylphenylthio)-acetaldehyde dimethyl acetal (Section IV, B).⁶¹⁷ The product previously described⁵⁴² as 6-hydroxy-3-phenylbenzo[*b*]thiophene has now been shown to be the 2-phenyl isomer.³⁰⁷ 6-Methoxy-⁶¹⁸ and 6-methoxy-5-methyl-benzo[*b*]thiophene⁶¹⁷ are demethylated by pyridine hydrochloride.

6-Alkoxybenzo[*b*]thiophenes undergo electrophilic substitution in the 2-position. Thus, 6-ethoxybenzo[*b*]thiophene affords its 2-bromo, 2-formyl, and 2-acetyl derivatives on bromination, Vilsmeier-Haack formylation, and Friedel-Crafts acetylation, respectively,⁴²⁴ and 6-methoxybenzo[*b*]thiophene undergoes Friedel-Crafts reaction with β -carbomethoxypropionyl chloride in the 2-position.⁶¹⁸

6. 7-Hydroxybenzo[*b*]thiophenes

7-Methoxybenzo[*b*]thiophene may be prepared by cyclodehydration of (*o*-methoxyphenylthio)acetaldehyde dimethyl acetal (Section

⁶¹⁷ A. V. Sunthakar and B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 35 (1951).

⁶¹⁸ M. K. Bhattacharjee, R. B. Mitra, B. D. Tilak, and M. R. Venkiteswaren, *Tetrahedron* **10**, 215 (1960).

IV, B).⁶¹⁷ On demethylation with pyridine hydrochloride, it affords the free phenol which is reported to be unstable.⁶¹⁷ A similar demethylation of 4-ethyl-2,3-dimethyl-7-methoxybenzo[*b*]thiophene affords the corresponding phenol.⁶¹⁵ 7-Hydroxybenzo[*b*]thiophene undergoes a Bucherer reaction to give 7-aminobenzo[*b*]thiophene.⁸⁴

7. *Dihydroxybenzo[*b*]thiophenes*

The synthesis of a number of dialkoxybenzo[*b*]thiophenes by ring closure is described in Section IV, D, and a number of reactions of alkoxy-substituted thioindoxyls has been discussed in Section VI, I, 2.

5,6-Dimethoxy-,^{291, 326, 339} 4,5-dimethoxy-,¹⁸⁹ 5,6-diethoxy-,³⁴¹ and 5,6-methylenedioxybenzo[*b*]thiophene¹⁸⁹ may be prepared by decarboxylation of the corresponding 2-carboxylic acid (Section IV, E). Demethylation of 5,6-dimethoxybenzo[*b*]thiophene with pyridine hydrochloride affords the 5,6-dihydroxy compound.³²⁶ The unstable 4,7-dihydroxybenzo[*b*]thiophene is obtained by catalytic reduction of benzo[*b*]thiophene-4,7-quinone.⁶¹⁹

5,6-Dimethoxy- and 5,6-methylenedioxybenzo[*b*]thiophene undergo bromination, Vilsmeier-Haack formylation, and Friedel-Crafts acetylation in the 2-position (see Section VI, A).¹⁸⁹ With nitric acid, however, 5,6-methylenedioxybenzo[*b*]thiophene affords an unidentified mononitro derivative, which is not the 2-nitro compound.⁵⁴⁸

8. *Trihydroxybenzo[*b*]thiophenes*

5,6,7-Trimethoxybenzo[*b*]thiophene may be prepared by decarboxylation of the corresponding 2-carboxylic acid (Section IV, E).³⁴¹

J. DERIVATIVES WITH A HYDROXYL GROUP IN A SIDE CHAIN

Hydroxymethylbenzo[*b*]thiophenes are most conveniently prepared by reduction with lithium aluminum hydride of the corresponding carboxylic acid^{78, 190, 337, 485, 486, 521, 528, 540} or ester.^{77, 87, 336, 337, 521, 526} Less frequently, they are prepared by reduction of the corresponding aldehyde^{100, 487} or acid chloride,⁵¹⁸ with sodium borohydride, or, in the case of 2-hydroxymethylbenzo[*b*]thiophenes, by reaction of the 2-lithium derivative with formaldehyde.^{90, 528} 3-Hydroxymethylbenzo[*b*]thiophene has been prepared from the corresponding aldehyde by means of a crossed Cannizzaro reaction

⁶¹⁹ A. Blackhall and R. H. Thomson, *J. Chem. Soc.* 3916 (1954).

with formaldehyde.⁴⁸⁷ 2,3-Di(hydroxymethyl)benzo[b]thiophene is obtained from 2,3-di(chloromethyl)benzo[b]thiophene by reaction with potassium acetate, and subsequent hydrolysis of the resulting di(acetoxymethyl) compound.⁵²⁷

2-(2-Benzo[b]thienyl)ethanol may be obtained by the action of ethylene oxide on 2-benzo[b]thienylsodium⁵²⁹; other 2-(benzo[b]thienyl)ethanols are readily prepared by the action of ethylene oxide on the appropriate benzo[b]thienylmagnesium halide.^{193, 447, 470} Treatment of 3-benzo[b]thienylmagnesium bromide with propylene oxide⁴⁹⁹ or trimethylene oxide⁵⁰⁰ gives 3-(3-benzo[b]thienyl)propan-2-ol and 3-(3-benzo[b]thienyl)propan-1-ol, respectively. 2-(Benzo[b]thienyl)ethanols^{143, 313, 485} and 3-(3-benzo[b]thienyl)propan-1-ol⁴⁸⁵ may also be obtained in good yield by reduction of the corresponding carboxylic acid or ester with lithium aluminum hydride.

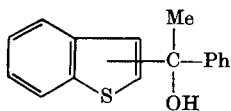
Reaction of 2-benzo[b]thienyllithium (and its 7-methyl derivative⁹⁰) with aldehydes^{486, 564, 620} or ketones^{467, 483} affords a secondary or tertiary alcohol, respectively. Treatment of 2-benzo[b]thienyllithium with acetyl chloride gives mainly 1,1-di(2-benzo[b]thienyl)ethylene.¹³² Side-chain alcohols in positions other than the 2-position are most easily prepared by reaction of the appropriate benzo[b]thienylmagnesium halide with aldehydes^{469, 471} or ketones,^{186, 309, 349, 467, 469, 479, 498} or by reaction of a benzo[b]thiophene aldehyde, ketone, or ester with an alkylmagnesium halide.^{358, 427, 465} The preparation of alcohols from 2- and 3-benzo[b]thienylmethylmagnesium chloride^{485, 528} is discussed in Section VI, D, 4.

Benzo[b]thienylketones are reduced by lithium aluminum hydride to secondary alcohols.^{465, 526} The carbinol bases of a series of benzo[b]thiophene analogs of malachite green have been prepared.⁶²¹

Benzo[b]thienylethylenes are readily obtained by elimination of water from the appropriate alcohol. For example, 3-vinylbenzo[b]thiophene is conveniently prepared by heating 1-(3-benzo[b]thienyl)ethanol with potassium hydrogen sulfate^{469, 471} or by heating 2-(3-benzo[b]thienyl)ethanol with molten alkali.⁴⁷⁰ 2-Vinylbenzo[b]thiophene is obtained by pyrolyzing the acetate of 1-(2-benzo[b]thienyl)ethanol.^{466, 620} Other benzo[b]thiophene alcohols have been dehydrated by heating them with oxalic acid,⁴⁸³ iodine,^{358, 465, 467, 528} or potassium hydrogen sulfate,^{465, 467} or alone.^{349, 485}

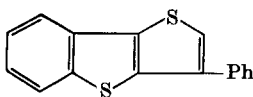
⁶²⁰ C. Kaiser and C. L. Zirkle, U.S. Patent 3,010,971 (1960); *Chem. Abstr.* **56**, 15484 (1962).

⁶²¹ V. V. Ghaisas, B. J. Kane, and F. F. Nord, *J. Org. Chem.* **23**, 560 (1958).

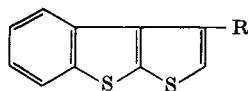


(248a) 2-isomer

(248b) 3-isomer



(249)

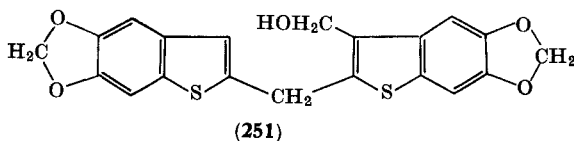


(250)

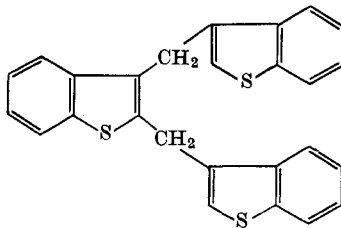
Heating 1-(2-benzo[*b*]thienyl)-1-phenylethanol (**248a**) with sulfur at 220° gives **249**; under similar conditions, 1-(3-benzo[*b*]thienyl)-1-phenylethanol (**248b**) gives **250** (R = Ph).⁴⁶⁷

The hydroxyl group of the side-chain alcohols is readily replaced by halogen by treatment with thionyl chloride^{87, 190, 336, 486, 526, 528, 529} or by treatment with phosphorus tribromide in chloroform^{193, 439, 447, 499, 500, 518} or ether,^{77, 527} or alone.⁴⁹⁶

When 2-hydroxymethyl-5,6-methylenedioxybenzo[*b*]thiophene is heated in a polar solvent with a catalytic amount of mineral acid, the polycyclic compound (**166**) is formed in 75% yield, probably by way of the intermediate (**251**).¹⁹⁰ 3-Hydroxymethylbenzo[*b*]thiophene and di(3-benzo[*b*]thienyl)methane react together in the presence of boron trifluoride to give a compound with the probable structure **252**.⁴⁸⁶



(251)

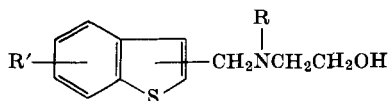


(252)

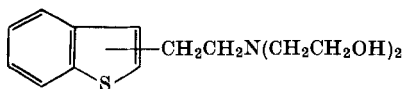
Nitration of 2-acetoxymethylbenzo[*b*]thiophene, followed by acidic hydrolysis of the product, affords 2-hydroxymethyl-3-nitrobenzo[*b*]thiophene.⁵¹⁸

Many amino alcohols of the type **253** have been prepared for pharmacological evaluation, by reaction of the appropriate 2- or

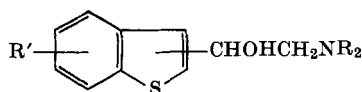
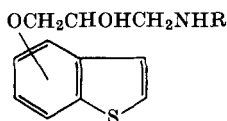
3-halomethylbenzo[b]thiophene with an *N*-substituted ethanol-amine.^{292, 298, 336, 491, 522, 523, 622} The amino alcohols (254) are prepared from 2- or 3-(2-chloroethyl)benzo[b]thiophene by an analogous reaction.⁵⁰⁹ *N,N*-Dialkyl-2-(2- or 3-benzo[b]thienyl)-2-hydroxyethylamines (255) are readily prepared by reduction of the corresponding ketone with either lithium aluminum hydride⁶²³ or sodium borohydride,^{218, 336, 557, 622} or by interaction of the appropriate (1,2-epoxyethyl)benzo[b]thiophene and an amine.^{336, 624} The amino-alcohols (256; side chain in 4- or 5-position) are prepared by reaction of the appropriate chlorohydrin or epoxide with a primary amine.⁶¹³ Reduction of the appropriate Mannich bases of 5-chloro- or 5-bromo-3-acetylbenzo[b]thiophene with sodium borohydride affords the amino alcohols (257).¹⁴⁴



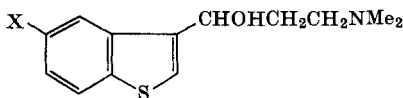
(253) R = alkyl, R' = alkyl or halogen



(254)

(255) NR₂ = NMe₂, NEt₂, N(CH₂Ph)₂, pyrrolidino, piperidino, or morpholino; R' = alkyl or halogen

(256)



(257) X = Br or Cl

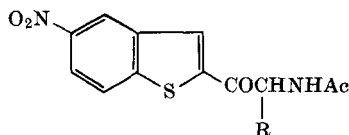
The amino alcohols described above are readily converted into the corresponding chloroamines by reaction with phosphorus pentachloride⁵²² or thionyl chloride^{144, 292, 298, 336, 491, 523, 622} in chloroform.

⁶²² N. B. Chapman, K. Clarke, and B. Iddon, *J. Med. Chem.* **9**, 819 (1966).

⁶²³ F. Sauter and L. Golser, *Monatsh. Chem.* **98**, 2039 (1967).

⁶²⁴ Smith, Kline & French Lab., British Patent 1,058,468 (1967); *Chem. Abstr.* **66**, 115592 (1967).

Treatment of the ketone (**258a**) with formaldehyde in the presence of sodium bicarbonate gives the alcohol (**258b**), the keto group of which is readily reduced by sodium borohydride to the corresponding secondary alcohol.²¹⁸



(**258a**) R = H

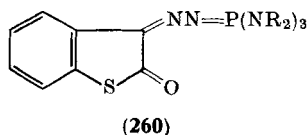
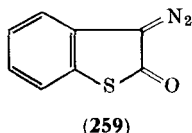
(**258b**) R = CH₂OH

K. BENZO[*b*]THIOPHENEQUINONES

1. Benzo[*b*]thiophene-2,3-quinones

The usual procedure for the preparation of benzo[*b*]thiophene-2,3-quinones, which involves acidic hydrolysis of an anil obtained from a thioindoxyl and an aromatic nitroso compound (usually *p*-nitroso-*N,N*-dimethylaniline), has been used to prepare 5-methyl-,⁶²⁵ 5-chloro-,¹¹⁷ and 5- and 6-nitrobenzo[*b*]thiophene-2,3-quinone.⁶²⁶

Oxidation of 5-chlorobenzo[*b*]thiophene-2,3-quinone with hydrogen peroxide in the presence of ammonia gives 5-chloro-1,2-benzisothiazole-3-carboxamide (**179d**).¹¹⁷



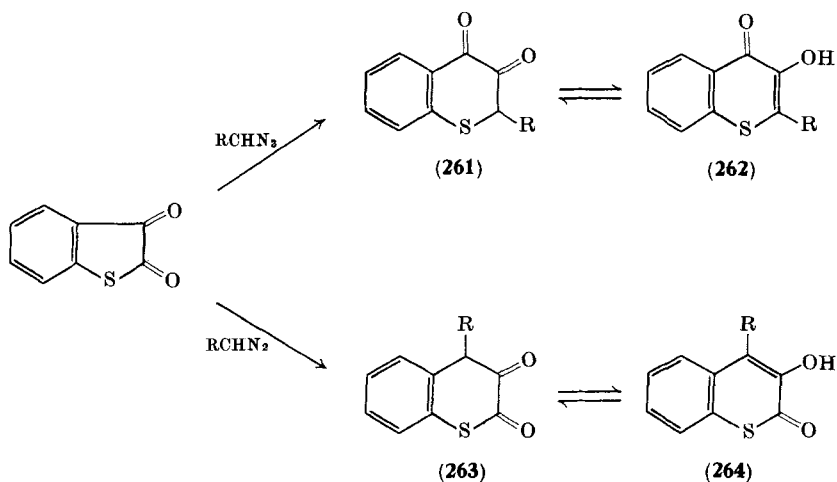
On treatment with base, the 3-*p*-tosylhydrazone of benzo[*b*]thiophene-2,3-quinone affords 3-diazobenzo[*b*]thiophen-2-one (**259**) which reacts with triaminophosphines to give the *o*-quinone triaminophosphazines (**260**; NR₂ = NMe₂, morpholino, or piperidino),⁶²⁷ and with phenols to give azo dyes.⁶²⁸

⁶²⁵ D. Walker and J. Leib, *J. Org. Chem.* **28**, 3077 (1963).

⁶²⁶ N. S. Dokunikhin and Yu. E. Gerasimenko, *Zh. Obshch. Khim.* **30**, 1231 (1960); *Chem. Abstr.* **55**, 507 (1961).

⁶²⁷ W. Ried and H. Appel, *Ann. Chem.* **679**, 56 (1964).

⁶²⁸ W. Ried and R. Dietrich, *Chem. Ber.* **94**, 387 (1961).



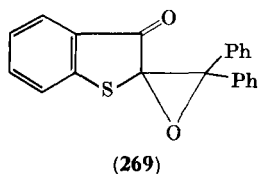
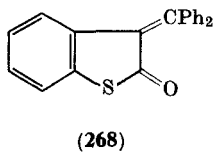
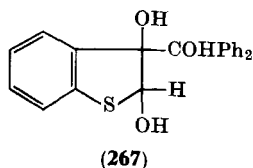
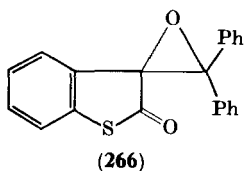
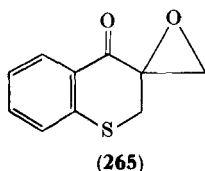
SCHEME 6

Eistert and Selzer⁶²⁹ have reported a number of interesting ring expansion reactions of benzo[*b*]thiophene-2,3-quinone with diazomethane, diazoethane, phenyldiazomethane, and ethyl diazoacetate; these are outlined in Scheme 6. The diazo carbon atom prefers to insert itself between the sulfur atom and the 2-position of the thiophene ring, to give derivatives of 1-thio-3-chroman-2-ol (3-hydroxy-1-thiochromanone) (262) through formation of 261. Ring expansion also occurs in some cases to give small amounts of 4-substituted 3-hydroxy-1-thiocoumarins (264) through formation of 263. Although this latter type of ring-expansion reaction is relatively unimportant in the case of benzo[*b*]thiophene-2,3-quinone, the corresponding indole and benzofuran compounds prefer to react in this way. The initial product (262; R = H) from the reaction of diazomethane with benzo[*b*]thiophene-2,3-quinone reacts further with an excess of diazomethane to give 265. The related compound (266) may be prepared by treating an ethereal solution of benzo[*b*]thiophene-2,3-quinone with diphenyldiazomethane.^{630, 631} Its structure was proved by reduction with lithium aluminum hydride to 267 which was rapidly dehydrated *in situ* to give 268; compound 268 was synthesized unambiguously by treating 3-diazobenzo[*b*]thiophen-2-one (259) successively with thio-

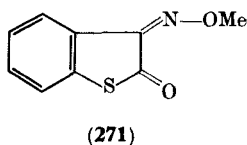
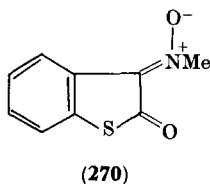
⁶²⁹ B. Eistert and H. Selzer, *Chem. Ber.* **96**, 1234 (1963).

⁶³⁰ A. Schönberg, K. Junghans, and E. Singer, *Tetrahedron Letters* 4667 (1966).

⁶³¹ A. Schönberg and K. Junghans, *Chem. Ber.* **99**, 1241 (1966).



benzophenone and copper bronze. The isomer (269) of 266 has been prepared by condensation of thioindoxyl with dichlorodiphenylmethane, followed by oxidation of the resulting product (29; R = R' = Ph) to 269 with alkaline peroxide. Benzo[*b*]thiophene-2,3-quinone reacts with diphenyldiazomethane in methanol to give an unidentified product, which is different from 266.⁶³⁰



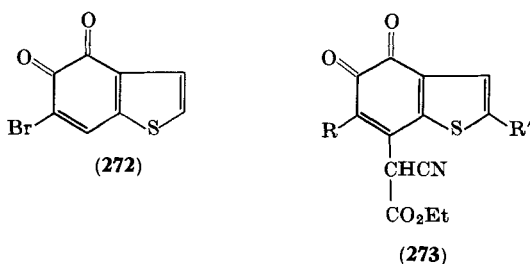
The *N*-methyl nitrosonium (270) is obtained by reaction of benzo[*b*]thiophene-2,3-quinone 3-oxime with diazomethane, or by treating the parent quinone with *N*-methylhydroxylamine.⁶³² With *O*-methylhydroxylamine, benzo[*b*]thiophene-2,3-quinone affords 271.⁶³²

⁶³² B. Eistert, R. Müller, H. Selzer, and E.-A. Hackmann, *Chem. Ber.* **97**, 2469 (1964).

Benzo[b]thiophene-2,3-quinone 2-oxime⁶³³ and 2-oxime 3-thiosemicarbazone²²⁰ form complexes with various metal ions.

2. Benzo[b]thiophene-4,5-quinones

6-Bromobenzo[b]thiophene-4,5-quinone (**272**) is obtained by the



action of nitric acid in chloroform on 4,6-dibromo-5-hydroxybenzo[b]thiophene.^{422, 497} Earlier, this quinone was reported to be 3-bromobenzo[b]thiophene-4,5-quinone.⁶³⁴ It readily condenses with ethyl cyanoacetate in the presence of triethylamine and potassium ferricyanide (Craven's⁶³⁵ test for quinones) to give 7-(carbethoxycyanomethyl)benzo[b]thiophene-4,5-quinone (**273**; R = R' = H) with loss of bromine from the 6-position; curiously, in the absence of potassium ferricyanide, bromine is retained to give **273** (R = Br, R' = H).⁴⁹⁷ If the crude quinone resulting from oxidation of 4,6-dibromo-5-hydroxybenzo[b]thiophene with nitric acid is used directly in the condensation with ethyl cyanoacetate in the presence of base and ferricyanide, two products are obtained; one of these is **273** (R = R' = H) and the other is its 2-bromo derivative (**273**; R = H, R' = Br).⁴⁹⁷ The latter product is formed by attack in the 2-position by the bromine released from the 6-position, to give 2,6-dibromobenzo[b]thiophene-4,5-quinone. This quinone then condenses with ethyl cyanoacetate with loss of bromine from the 6-position under these reaction conditions. It has been isolated and shown to react in this way. Hydrogenation of **273** (R = H, R' = Br), followed by oxidation of the product (**274**) affords **273** (R = R' = H). Other 7-(carbethoxycyanomethyl)benzo[b]thio-

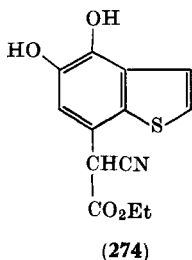
⁶³³ V. Hovorka and J. Morávek, *Chem. Listy* **46**, 545 (1952); *Collection Czech. Chem. Commun.* **18**, 53 (1953); *Chem. Abstr.* **47**, 8060 (1953).

⁶³⁴ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 104. Wiley (Interscience), New York, 1954.

⁶³⁵ R. Craven, *J. Chem. Soc.* 1605 (1931).

phene-4,5-quinones may be prepared similarly by condensing the parent quinone with ethyl cyanoacetate in the presence of base.^{152, 421, 497}

7-(Carbethoxycyanomethyl)benzo[*b*]thiophene-4,5-quinone (**273**; $R = R' = H$)⁴⁹⁷ and its 3-bromo¹⁵² and 2-carboxy⁴⁹⁷ derivatives may be prepared also by reduction of the corresponding 5-hydroxy-4-nitroso(or 4-nitro)benzo[*b*]thiophene with Raney nickel and hydrazine in ethanol, to give an unstable 4-amino-5-hydroxybenzo[*b*]thiophene, which is oxidized directly *in situ* by ferricyanide in the presence of base and ethyl cyanoacetate. Under these conditions, condensation of the resulting quinone occurs before its decomposition.



7-(Carbethoxycyanomethyl)benzo[*b*]thiophene-4,5-quinones readily afford phenazines.⁴⁹⁷

Attempts to prepare 7-(cyanomethyl)benzo[*b*]thiophene-4,5-quinones by elimination of the carbethoxy group from a corresponding 7-(carbethoxycyanomethyl) compound have failed, except in one case; **273** ($R = H$, $R' = Br$) affords 2-bromo-7-(cyanomethyl)benzo[*b*]thiophene-4,5-quinone on treatment with Triton B (benzyltrimethylammonium hydroxide).⁴⁹⁷

On heating a solution of 3,4-dibromo-4-nitro-4,5-dihydrobenzo[*b*]thiophen-5-one (Section VI, I, 4) in benzene, 3-bromobenzo[*b*]thiophene-4,5-quinone is obtained.⁴⁹⁷ The unstable product readily condenses with ethyl cyanoacetate in the presence of base to give 3-bromo-7-(carbethoxycyanomethyl)benzo[*b*]thiophene-4,5-quinone. The 4-bromo-4-nitro-4,5-dihydrobenzo[*b*]thiophen-5-ones prepared by nitration of 3,4-dibromo-,^{152, 421} 4,6-dibromo-,¹⁵² 3,4,6-tribromo-,⁴²¹ and 2,3,4,6-tetrabromo-5-hydroxybenzo[*b*]thiophene⁴²¹ decompose similarly to the corresponding 4,5-quinones on being boiled in benzene.

3. Benzo[b]thiophene-4,7-quinones

5-Hydroxy-6- γ -cyclohexylpropylbenzo[b]thiophene-4,7-quinone is obtained by radical alkylation of 5-hydroxybenzo[b]thiophene-4,7-quinone.⁶³⁶

L. ALDEHYDES AND KETONES

1. Aldehydes

a. *Preparation.* Benzo[b]thiophene aldehydes may usually be obtained by one or more of the following general methods (Table XII): from the appropriate halomethyl compound by the Sommelet method (method a),^{78, 91, 105, 144, 343, 487, 520, 537} or by the Kröhnke method (method b),^{77, 144, 511} from the parent benzo[b]thiophene by Vilsmeier-Haack formylation with dimethylformamide^{132, 183, 189, 424, 637} or *N*-methylformanilide^{93, 436, 537, 637-639} in the presence of phosphorus oxychloride (method c), or by the action of *N*-methylformanilide^{520, 621, 640} or dimethylformamide^{76, 78, 90, 105} on the appropriate benzo[b]-thienylmagnesium bromide or 2-benzo[b]thienyllithium (method d). Benzo[b]thiophene is less reactive than benzofuran⁶³⁷ in the Vilsmeier-Haack reaction, and gives the 3-aldehyde in only 9% yield.^{537, 637} The 2-position is activated toward formylation in 6-ethoxy-,⁴²⁴ 5,6-dimethoxy- and 5,6-methylenedioxy-,¹⁸⁹ and 3-ethylbenzo[b]thiophene (2-ethylbenzo[b]thiophene gives no pure products on formylation).¹³² Formylation of 3-methoxybenzo[b]thiophene at 45°-55° gives the 2-aldehyde^{93, 183}; at 95°, the methoxyl group is replaced by chlorine, and 3-chlorobenzo[b]thiophene-2-carboxaldehyde is obtained (90%).⁹³ Formylation of 4-methoxy-⁹³ or 2-methoxybenzo[b]thiophene¹⁸³ gives the 7- or 3-aldehyde, respectively. Reaction of 4,5,6,7-tetrahydro-2-benzo[b]thienylmagnesium iodide¹⁹³ or 5-benzo[b]thienylmagnesium iodide⁸⁷ with ethyl orthoformate gives the corresponding aldehyde in good yield.

Benzo[b]thiophene aldehydes have also been prepared by oxidation of the corresponding primary alcohol with *tert*-butyl chromate,⁵¹⁸ nitric acid,⁵¹⁸ or manganese dioxide,^{337, 565} and by reaction of the

⁶³⁶ L. F. Fieser, M. T. Leffler, and Co-workers, *J. Am. Chem. Soc.* **70**, 3212 (1948).

⁶³⁷ M. Bisagni, N. P. Buu-Hoi, and R. Royer, *J. Chem. Soc.* 3688 (1955).

⁶³⁸ F. Dallacker, E. Kaiser, and P. Uddrich, *Ann. Chem.* **689**, 179 (1965).

⁶³⁹ Ya. L. Gol'dfarb, S. Ozolins, and V. P. Litvinov, *Zh. Obshch. Khim.* **37**, 2220 (1967); *Chem. Abstr.* **68**, 87218 (1968).

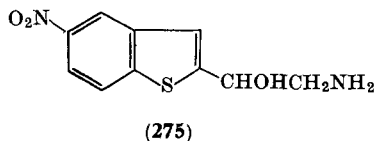
⁶⁴⁰ D. A. Shirley and M. J. Danzig, *J. Am. Chem. Soc.* **74**, 2935 (1952).

TABLE XII
 BENZO[b]THIOPHENE ALDEHYDES

Substituents	Melting point (°C)	Yield (%)	Method ^a	Ref.
2-CHO	42	43	a	91
	34-34.5	77, 62	d	520, 640
3-Br, 2-CHO	123-124	10	d	621
4-Br, 2-CHO	94-95	31	d	105
5-Br, 2-CHO	119-120	73	d	76
6-Br, 2-CHO	95-96	28	d	105
7-Br, 2-CHO	113-114	19	d	105
3-Cl, 2-CHO	106-107	?	d	621
3-Me, 2-CHO	88-88.5	55	d	621
7-Me, 2-CHO	40	79	d	90
3-Et, 2-CHO	71	21	c	132
2,3-(CHO) ₂	111-112	95	b	511
4,5,6,7-H ₄ , 2-CHO	Liquid	83	c	436
5,6-OCH ₂ O-, 2-CHO	166-167	66, 34	c	638, 189
5,6-OMe ₂ , 2-CHO	153-154	26	c	189
6-OEt, 2-CHO	99	34	c	424
3-OMe, 2-CHO	84-85	40-50, 96	c	93, 183
3-CHO	58	67, 62, 50	a	487, 91, 520
		7, 9	c	537, 637
4-Br, 3-CHO	144-145	52	a	105
5-Br, 3-CHO	108-109	63, 50	a	144, 105
		35	b	144
6-Br, 3-CHO	110-111	41	a	105
7-Br, 3-CHO	97-98	48	a	105
5-Cl, 3-CHO	105-106	66, 30	a, b	144
5-OCH ₂ Ph, 3-CHO	96-97	40	a	343
7-Me, 3-CHO	64	22, 55	a, d	78
2-SEt, 3-CHO	41-42	85	c	639
2-OMe, 3-CHO	59-60	72	c	183
4-CHO	34	50	a	91
5-CHO	57	43	a	91
6-CHO	43	62	a	91
		60	b	77
7-CHO	42	54	a	91
4-OMe, 7-CHO	111	70	c	93
3-Br, 7-CHO	111-111.5	62	a	91

^a See text for a discussion. (a) Sommelet method; (b) Kröhnke method; (c) Vilsmeier-Haack formylation; and (d) from lithium or magnesium derivative.

corresponding chloromethyl compound with cupric nitrate and nitric acid,³³⁷ or sodio-2-nitropropane.⁴⁸³ They have been indirectly prepared from the corresponding carboxylic acid by reduction of the acid chloride with lithium tri-*tert*-butoxyaluminumhydride³³⁷ or by reaction of the acyl toluene-*p*-sulfonylhydrazide at 160° with sodium



carbonate in ethylene glycol.⁵⁵⁶ 5-Nitrobenzo[b]thiophene-2-carboxaldehyde has been obtained by periodate oxidation of the amino-alcohol (275).²¹⁸ 4-Nitrobenzo[b]thiophene-2-carboxaldehyde is formed when 4-nitro-2-(β -nitrovinyl)benzo[b]thiophene is oxidized with permanganate.¹⁴¹ Reaction of 2,3-dimethylbenzo[b]thiophene with acetyl nitrate gives, *inter alia*, 3-methylbenzo[b]thiophene-2-carboxaldehyde (6%) (Section VI, E, 1, *a*).¹⁰⁰

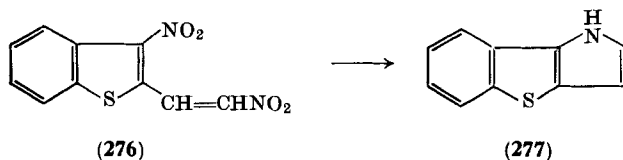
b. *Properties.* Benzo[b]thiophene aldehydes have the usual properties of aromatic aldehydes: in particular, they may be oxidized (Section VI, M) and reduced^{132, 436, 487}; they undergo the Cannizzaro reaction and benzoin condensation⁴⁸⁷; they react normally with Grignard reagents,^{417, 465} organolithium compounds,⁴⁸⁶ and Wittig reagents⁴⁶⁵; they form diacetoxymethyl compounds with acetic anhydride^{141, 477, 518}; they form the usual carbonyl derivatives^{144, 487, 641}; and they form Schiff's bases with amines.⁵⁶⁵ The oximes may be converted into nitriles by heating them with acetic anhydride.¹⁴⁴ Alternatively, the aldehyde may be directly converted into the nitrile by reaction with hydroxylamine hydrochloride, formic acid, and sodium formate,^{87, 144} or with diammonium hydrogen phosphate, 1-nitropropane, and acetic acid.⁴⁸³ Benzo[b]thiophene analogs of malachite green have been prepared from some substituted benzo[b]thiophene-2 and 3-carboxaldehydes.⁶²¹ Reaction of the 2-aldehyde with trimethylsulfoxonium iodide and sodium hydride,⁶²⁴ or with diazomethane,⁶⁴² gives 2-(1,2-epoxyethyl)benzo[b]thiophene. Re-

⁶⁴¹ R. Behnisch, F. Mietzsch, and H. Schmidt, U.S. Patent 2,775,593 (1956); *Chem. Abstr.* **51**, 8804 (1957).

⁶⁴² L. Capuano and U. Hahn-Riehn, *Chem. Ber.* **94**, 302 (1961).

action of benzo[*b*]thiophene-3-carboxaldehyde with diazomethane is said, however, to yield 3-benzo[*b*]thienylacetone (100%).⁶⁴³ Treatment of the diethyl acetal of 2-ethylthiobenzo[*b*]thiophene-3-carboxaldehyde with sodamide affords 3-iminomethyl-2-mercapto-benzo[*b*]thiophene.⁶³⁹

Benzo[*b*]thiophene aldehydes have been condensed with a variety of "active methylene" compounds, including cyclic^{511, 644} and open-chain⁶⁴⁵⁻⁶⁴⁷ ketones, aliphatic aldehydes,⁹⁰ benzyl cyanides,^{93, 436} malononitrile,⁴⁸⁷ rhodanine,^{144, 648} hippuric acid,⁴⁷⁷ barbituric acid,⁴⁸⁷ diethyl malonate,⁴⁸⁷ and malonic acid (Section VI, M). Aliphatic nitro compounds condense smoothly with most benzo[*b*]thiophene aldehydes^{93, 141, 337, 343, 556, 649, 650} (except 5-hydroxy- and



5-methanesulfonyloxybenzo[*b*]thiophene-3-carboxaldehyde³³⁷), and the products may be readily reduced to substituted β -benzo[*b*]thienylethylamines. 3-Nitro-2-(2-nitrovinyl)benzo[*b*]thiophene (**276**) yields [1]benzothieno[3,2-*b*]pyrrole (**277**) on reductive cyclization.⁶⁴⁹ The Hantzsch synthesis with ethyl acetoacetate and ammonia has been applied to benzo[*b*]thiophene-2-carboxaldehyde to yield the pyridine (**278**; R = H).⁶⁵¹ Cyclization of the intermediate dicarboxylic acid (**278**; R = CO₂H) with PPA yields **279**.⁶⁵² The condensation product

⁶⁴³ L. Capuano, *Chem. Ber.* **98**, 3187 (1965).

⁶⁴⁴ G. Saint-Ruf, N. P. Buu-Hoï, and P. Jacquignon, *J. Chem. Soc.* 3237 (1959).

⁶⁴⁵ W. Ried and G. Dankert, *Chem. Ber.* **90**, 2707 (1957).

⁶⁴⁶ W. Ried and W. Reitz, *Chem. Ber.* **89**, 2570 (1956).

⁶⁴⁷ Y. Suzuki, *Ann. Rept. Liberal Arts Sci. Fac. Iwate Univ.* **25**, 41 (1965); *Chem. Abstr.* **65**, 3820 (1966).

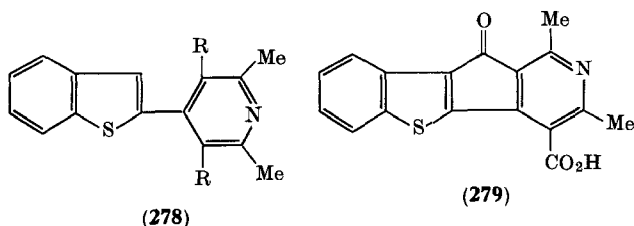
⁶⁴⁸ N. B. Chapman, C. G. Hughes, and R. M. Scrowston, unpublished work (1968).

⁶⁴⁹ O. P. Shkurko and V. P. Mamaev, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* 634 (1966); *Chem. Abstr.* **66**, 65410 (1967).

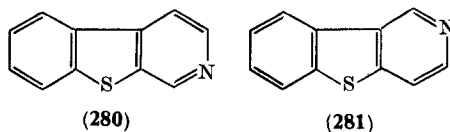
⁶⁵⁰ W. Ried, E. Köhler, and F. J. Königstein, *Ann. Chem.* **598**, 145 (1956).

⁶⁵¹ W. Treibs and J. Beger, *Ann. Chem.* **652**, 192 (1962).

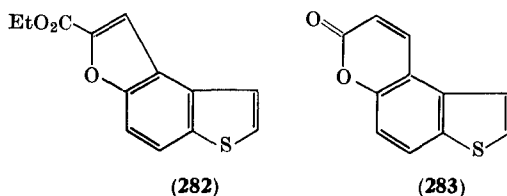
⁶⁵² J. Beger and W. Treibs, *Ann. Chem.* **652**, 204 (1962).



of benzo[b]thiophene-2- or 3-carboxaldehyde with aminoacetal can be cyclized with PPA to furnish the benzothienopyridines (**280** or **281**, respectively).⁶⁵³



5-Hydroxybenzo[b]thiophene-4-carboxaldehyde, which is prepared from 5-hydroxybenzo[b]thiophene by the Duff reaction³³⁸ or, better, by a modified Gattermann reaction,³⁴⁰ reacts with diethyl bromomalonate to give the thienobenzofuran (**282**), and undergoes the Perkin reaction to give the thienobenzo- α -pyrone (**283**).³³⁸



Matsuki and Lee⁹¹ have brominated all the isomeric benzo[b]thiophene aldehydes and obtained solely the 3-bromo compound, except with the 3-aldehyde; this observation has been confirmed by other workers in the case of the 2-aldehyde.⁴⁷⁷ Monobromination of 7-methylbenzo[b]thiophene-2-carboxaldehyde produces mainly the 3-bromo derivative (48%), together with significant amounts of the 4- (23%) and 6-isomer (29%).⁹⁰ The order of reactivity of the 3-, 4-, and 6-positions is reversed in the nitration of the unsubstituted

⁶⁵³ W. Herz and L. Tsai, *J. Am. Chem. Soc.* **75**, 5122 (1953).

benzo[b]thiophene-2-carboxaldehyde (in acetic anhydride); a mixture of 3- (10%), 4- (66%), and 6-nitroaldehydes (24%) (as the diacetates) is obtained.^{142, 518} Nitration of benzo[b]thiophene-2-carboxaldehyde diacetate gives a mixture of the 6- (26%), 4- (38%), and 3-nitro (36%) compounds.^{142, 518} An early claim⁴¹⁷ that nitration of benzo[b]thiophene-3-carboxaldehyde with fuming nitric acid in acetic acid gives the 2-nitro compound (60%) has not been substantiated by later workers.^{99, 654} On the contrary, Martin-Smith and Armstrong⁹⁹ have shown that nitration is confined to the benzene ring, and have isolated the four mononitro isomers. The strong deactivation of the 2-position by the 3-CHO group is further confirmed by the observations that benzo[b]thiophene-3-carboxaldehyde is not brominated, even under forcing conditions,⁹¹ and that 7-methylbenzo[b]thiophene-3-carboxaldehyde gives an approximately equal mixture of the 4- and 6-derivative on monobromination.⁷⁸

2. Friedel-Crafts Acylation

The earlier observations⁶⁵⁵ that Friedel-Crafts acylation of benzo[b]thiophene yields a mixture of the 2- and 3-ketone, in which the 3-isomer predominates, has been confirmed by reaction of benzo[b]thiophene with a variety of acid chlorides,^{132, 464, 465, 485, 501, 502, 512, 650, 656-658} ester chlorides,^{135, 439, 500, 659} and acid anhydrides^{439, 500, 620, 660, 661} (Table XIII).

Acylation (particularly acetylation) of simple alkylbenzo[b]thiophenes has been extensively studied. Acylation of 2-methyl-,^{98, 528, 623, 654, 660} 2-ethyl-,^{132, 464, 662, 663} 3-methyl-,^{98, 485, 660, 664} 3-ethyl-,^{132, 464,}

⁶⁵⁴ D. A. Shirley, B. H. Gross, and M. J. Danzig, *J. Org. Chem.* **23**, 1024 (1958).

⁶⁵⁵ H. B. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 116. Wiley (Interscience), New York, 1954.

⁶⁵⁶ A. W. Chow and J. R. E. Hoover, U.S. Patent 3,210,337 (1965); *Chem. Abstr.* **64**, 8189 (1966).

⁶⁵⁷ G. M. Badger and B. J. Christie, *J. Chem. Soc.* 913 (1958).

⁶⁵⁸ G. M. Badger and B. J. Christie, *J. Chem. Soc.* 3435 (1956).

⁶⁵⁹ R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. (India)* **15B**, 497 (1956).

⁶⁶⁰ M. Pailer and E. Romberger, *Monatsh. Chem.* **92**, 677 (1961).

⁶⁶¹ E. Campaigne, E. D. Weinberg, G. Carlson, and E. S. Neiss, *J. Med. Chem.* **8**, 136 (1965).

⁶⁶² R. Royer, P. Demerseman, J.-P. Lechartier, and A. Cheutin, *Bull. Soc. Chim. France* 1711 (1962).

⁶⁶³ R. Royer, P. Demerseman, and J.-P. Lechartier, *Compt. Rend.* **254**, 2605 (1962).

⁶⁶⁴ P. Faller and P. Cagniant, *Bull. Soc. Chim. France* 30 (1962).

TABLE XIII

FRIEDEL-CRAFTS ACYLATION OF ALKYL, ALKOXY, HALO, AND HYDRO BENZO[b]THIOPHENES*

Acylating agent	Catalyst	Starting material (substituents)	Product	Melting point (°C)	Yield (%)	Ref.
Ac ₂ O	BF ₃	2-Me	3-COMe	69	90, 74	623, 98, 528
Ac ₂ O	H ₂ SO ₄	2-Me	3-COMe	71-72	10	660
Ac ₂ O	SnCl ₄	2-Me	3-COMe	67-69	39	654
PhCOCl	SnCl ₄	2-Me	3-COPh	75-76	?	528
AcCl	SnCl ₄	2-Et	3-COMe	ca. 25	93	132
PhCOCl	SnCl ₄	2-Et	3-COPh	Oil	76	132
<i>p</i> -MeOC ₆ H ₄ COCl	SnCl ₄	2-Et	3-(COC ₆ H ₄ OMe- <i>p</i>)	70	93	464, 663
Ac ₂ O	BF ₃	3-Me	2-COMe	76.5-77.5	44, 62	485, 98
AcCl	AlCl ₃	3-Me	2-COMe	78	?	664
Ac ₂ O	H ₂ SO ₄	3-Me	2-COMe	77-78	10	660
AcCl	SnCl ₄	3-Et	2-COMe	60.5	94	132
AcCl	AlCl ₃	3-Et	2-COMe	62	80	664
PhCOCl	SnCl ₄	3-Et	2-COPh	Liquid	80	132
<i>p</i> -MeOC ₆ H ₄ COCl	SnCl ₄	3-Et	2-(COC ₆ H ₄ OMe- <i>p</i>)	94	90	464
Ac ₂ O	BF ₃	4-Me	2-COMe	103-104	(81)	98
			3-COMe	—	61 ^b	
			2-COMe	109-110	(19)	
Ac ₂ O	BF ₃	5-Me	2-COMe	—	(15)	98
			3-COMe	90-92	65 ^b	
Ac ₂ O	BF ₃	6-Me	2-COMe	121	(85)	98
			2-COMe	88.5	69	
Ac ₂ O	BF ₃	7-Me	2-COMe	—	(19)	98
			3-COMe	72-73	68 ^b	
					(81)	

continued

TABLE XIII—*continued*

Acylating agent	Catalyst	Starting material (substituents)	Product	Melting point (°C)	Yield (%)	Ref.
Ac ₂ O	BF ₃	3,5-Me ₂	2-COMe	84.5–85.5	75	82
AcCl	AlCl ₃	3,5-Me ₂	2-COMe	88	78	664
Ac ₂ O	BF ₃	2,5-Me ₂	3-COMe	78.5–79.5	72	82
Ac ₂ O	BF ₃	3,7-Me ₂	2-COMe	87.5–88.5	80	82
AcCl	AlCl ₃	2,3-Me ₂	6-COMe	64.5–65.5	(100) 65 ^b	136, 418
Ac ₂ O	BF ₃	2,3-Me ₂	6-COMe	64.5–65	70	82
			5-COMe	140–145 ^c		
			5-COMe	^a	(33)	
AcCl	AlCl ₃	2,3-Et ₂	6-COMe	^a	82 ^b (66)	132, 136
AcCl	AlCl ₃	2-Et, 3-Me	6-COMe	49.5	50	136
AcCl	AlCl ₃	3,4,7-Me ₃	2-COMe	81–82	ca. 70	139
AcCl	AlCl ₃	3,5,7-Me ₃	2-COMe	108	ca. 70	139
AcCl	AlCl ₃	2,3,5-Me ₃	6-COMe	66–68	95	136, 418
AcCl	AlCl ₃	2,3,7-Me ₃	6-COMe	98	55 ^c	136, 418
AcCl	AlCl ₃	2,3,4,7-Me ₄	6-COMe	115.5	ca. 70	139, 665
AcCl	AlCl ₃	2,3,5,7-Me ₄	6-COMe	83	ca. 70 ^c	139, 665
Ac ₂ O or AcCl	FeCl ₃ or AlCl ₃	5-Cl	3-COMe	80–82	70	144
			2-COMe	88–90	5	
AcCl	AlCl ₃	5-Br	3-COMe	91–92	80, 79 ^f	76, 144
AcCl	AlCl ₃	4,5,6,7-F ₄	3-COMe	132–134	85 ^e	103

AcCl	AlCl ₃	2,3-Br ₂	6-COMe	132	86	77
AcCl	AlCl ₃	2-Br, 3-Me	4-COMe	123-124	10	102
AcCl	AlCl ₃	3-Br, 2-Me	6-COMe	114-115	67 ^a	102
Ac ₂ O	SnCl ₄	6-OEt	2-COMe	96-97	94	102
Ac ₂ O	SnCl ₄	5,6-(OMe) ₂	2-COMe	107-108	80	424
Ac ₂ O	SnCl ₄	5,6-OCH ₂ O-	2-COMe	131-132	80	189
Ac ₂ O	BF ₃	2-OMe	2-COMe	169-170	67	189
Ac ₂ O	BF ₃	3-OMe	3-COMe	112-113	87.5	183
AcCl	SnCl ₄	4-OMe	2-COMe	66-67	50	183
AcCl	SnCl ₄	2-Et, 4-OMe	7-COMe	133.5	0.5	614
AcCl	SnCl ₄	7-Et, 4-OMe	2-COMe	112	85	614
AcCl	AlCl ₃	2,3-H ₂	5-COMe	52.5	89	614
AcCl	AlCl ₃	4,5,6,7-H ₄	2-COMe	79.5	60	614
EtCOCl	AlCl ₃	4,5,6,7-H ₄	2-COEt	44-45	33, 54	192, 427
AcCl	SnCl ₄	2-Me, 4,5,6,7-H ₄	3-COMe	Liquid	80	194
AcCl	AlCl ₃	2-Et, 4,5,6,7-H ₄	3-COMe	33.5	90	193
				Liquid	80-85	436
				Liquid	50	194

^a For convenience, the acylation of benzo[b]thiophene is omitted from this table. References are given in Section VI,L,2.

^b The main entry is the total yield of ketonic material. The percentage composition of the mixture is given in parentheses.

^c This melting point corresponds to that of 5,6-diacetyl-2,3-dimethylbenzo[b]thiophene.

^d The mixture was not separated.

^e A small amount of an isomer was also formed.

^f The 2-isomer was also formed, but it was not purified.

^g 2-Acetyl-3-methylbenzo[b]thiophene was also formed (23%).

⁶⁶⁴ 2-benzyl-, ^{132, 519} and 2-anisylbenzo[*b*]thiophene ⁴⁶⁴ always proceeds in the vacant thiophene position. 3-Anisylbenzo[*b*]thiophene resisted acetylation under the conditions used, probably for steric reasons. ⁴⁶⁴ Acetylation of 5-^{98, 660} and 7-methylbenzo[*b*]thiophene ⁹⁸ gives a mixture of the 2- and 3-ketone, in which the 3-isomer predominates. Acetylation of 4- or 6-methylbenzo[*b*]thiophene gives mainly the 2-ketone, together with small amounts of the 3-isomer with the 4-methyl compound. ⁹⁸

Di-^{82, 664} and trimethylbenzo[*b*]thiophenes ¹³⁹ with only one substituent in the thiophene ring undergo acetylation in the remaining thiophene position, 2,3-Dimethyl-, ^{82, 136, 418} 2,3-diethyl-, ^{132, 136, 464} and 2-ethyl-3-methyl-benzo[*b*]thiophene ¹³⁶ give mainly the 6-ketone on acylation, together with smaller amounts of the 5-isomer in some cases. Prolonged acetylation of 2,3-dimethylbenzo[*b*]thiophene gives the 5,6-diacetyl compound (15%). ¹³⁶ 2,3,4-, ¹³⁶ 2,3,5-, ^{136, 418} and 2,3,7-trimethylbenzo[*b*]thiophenes ^{136, 418} are acetylated solely in the 6-position. When the 6-position is occupied, as in 2,3,6-trimethyl- ¹³⁶ or 2,3,6-triethylbenzo[*b*]thiophene, ¹³² the acetyl group enters the 5-position. Tetramethylbenzo[*b*]thiophenes are likewise acetylated in the 6-position if this is free ^{139, 665}; with 2,3,5,7-tetramethylbenzo[*b*]thiophene a small amount of by-product may be the 4-isomer. ^{139, 665}

Friedel-Crafts acylation of halobenzo[*b*]thiophenes has been much less extensively studied. Acetylation of 5-bromo-, ^{76, 144} 5-chloro-, ¹⁴⁴ and 4,5,6,7-tetrafluorobenzo[*b*]thiophene ¹⁰³ gives mainly the 3-acetyl compound in each case, together with less than 10% of the 2-isomer in some cases. ^{103, 144} 2,3-Dibromobenzo[*b*]thiophene affords mainly the 6-ketone on acetylation. ⁷⁷ Similarly, the 6-ketone is the major (94%) product formed by acetylation of 3-bromo-2-methylbenzo[*b*]thiophene at 0°; raising the temperature to 10° results in replacement of the bromine atom by an acetyl group, to give mainly (80%) 3-acetyl-2-methylbenzo[*b*]thiophene. ¹⁰² 2-Bromo-3-methylbenzo[*b*]thiophene is not acetylated at 0°; at 25° a mixture of the 6-acetyl compound (67%), its 4-isomer (10%), and 2-acetyl-3-methylbenzo[*b*]thiophene (23%) is obtained. ¹⁰²

Acylation of 2- or 3-methoxybenzo[*b*]thiophene in the presence of boron trifluoride takes place in the free thiophene position ¹⁸³; concomitant demethylation may occur in the presence of aluminum chloride. ^{272, 666} Attempted acetylation of 3-bromo-2-methoxybenzo-

⁶⁶⁵ P. Faller and P. Cagniant, *Compt. Rend.* **254**, 1447 (1962).

⁶⁶⁶ Aktiebolag Hassle, Apotekare Paul Nordstroms Fabriker, Netherlands Patent Appl. 6,607,608 (1966); *Chem. Abstr.* **67**, 43677 (1967).

[b]thiophene in the presence of aluminum chloride gives a low yield of 3-acetyl-2-methoxybenzo[b]thiophene and a large amount of polymeric material.¹⁸³ Similar treatment of 2-bromo-3-methoxybenzo[b]thiophene gives mainly thioindigo, owing to reaction of the catalyst with the starting material.¹⁸³ The 2-position is unexpectedly the most reactive toward Friedel–Crafts acetylation in 5,6-dimethoxy-, 5,6-methylenedioxy-,¹⁸⁹ 6-methoxy-,⁶¹⁸ and 6-ethoxybenzo[b]thiophene.⁴²⁴ A 4-methoxy group, however, directs substitution mainly into the 7-position, with the formation of very little (0.5%) 2-ketone; if the 7-position is occupied, reaction takes place exclusively in the 2-position.⁶¹⁴

5-Acetoxybenzo[b]thiophene gives the 3-acetyl compound on acetylation.³³⁷

2,3-Dihydrobenzo[b]thiophene undergoes acetylation^{192, 427} and succinoylation⁴²⁶ in the 5-position. 4,5,6,7-Tetrahydrobenzo[b]thiophene is acylated in the 2-position,^{193, 194, 436, 439, 440} or, when this is occupied by an alkyl group, in the 3-position.^{194, 436}

3. Ketones

a. *Preparation.* Benzo[b]thienyl alkyl and aryl ketones are most readily prepared by Friedel–Crafts acylation of the appropriate benzo[b]thiophene (Section VI, L, 2). Aryl ketones are prepared less often by Friedel–Crafts acylation of the appropriate aromatic hydrocarbon with a benzo[b]thiophenecarbonyl chloride.^{132, 464}

Reaction between an acid chloride and diethyl ethoxymagnesium-malonate provides a useful route to acetylbenzo[b]thiophenes^{144, 218, 336, 557} and benzo[b]thienylacetones¹⁰¹ (method a). Treatment of a benzo[b]thienylmagnesium bromide^{344, 478, 495, 501–504} or a benzo[b]thienyllithium⁵⁰⁴ with a nitrile or, conversely, treatment of a cyano-benzo[b]thiophene with an alkylmagnesium halide^{81, 434, 512} gives a ketimine, hydrolysis of which yields the appropriate ketone in good yield (method b). 3-Cyanobenzo[b]thiophene and *tert*-butylmagnesium chloride give the expected ketimine,⁵¹² which rearranges in the presence of acid to give 2-*tert*-butyl-3-cyano-2,3-dihydrobenzo[b]thiophene.⁴³⁴ Methyl ketones may be conveniently prepared by the action of dimethylcadmium on a benzo[b]thiophenecarbonyl chloride (method c).^{76, 90, 654} Long-chain keto esters have been obtained by reaction of di(3-benzo[b]thienyl)cadmium and the appropriate ester chloride.¹³⁵ The action of lithium acetate^{464, 614, 654} or lithium benzoate¹³² on the appropriate 2-benzo[b]thienyllithium gives the

corresponding 2-acetyl- or 2-benzoylbenzo[*b*]thiophene, respectively, in good yield (method d). Ketones prepared by the above methods are collected in Table XIV.

TABLE XIV

BENZO[*b*]THIENYL KETONES (OTHER THAN THOSE PREPARED BY FRIEDEL-CRAFTS ACYLATION)^a

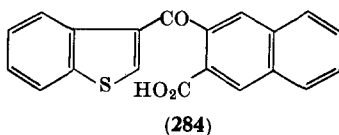
Substituents	Melting point (°C)	Yield (%)	Method ^b	Ref.
2-COMe	88	54	d	464, 654
2-COMe, 5-NO ₂	172	70	a	218
2-COMe, 5-Cl	93-94	68	a	336
2-COMe, 5-Br	112-113	70, 61	a, c	336, 76
2-COMe, 7-Me	83-83.5	65	c	90
2-COMe, 4-OMe	133.5	83	d	614
3-COMe	64-65	15, 64	b, c	512, 654
3-COMe, 5-Cl	80-82	50	a	144
2-COPh	47.5	49	d	132
2-CO(C ₆ H ₄ - <i>o</i> -CH ₂ Ph)	110-111	66	b	504
5-COMe	63-65	ca. 50	a	557
5-COMe, 2,3-Me ₂	68	—	b	81
5-COMe, 2,3,4,7-Me ₄	92	88	b	81
6-COMe, 2,3,5-Me ₃	67	60	b	81
6-COMe, 2,3,4,7-Me ₄	115.5	—	b	81
3-CH ₂ COMe	Liquid	85	a	101
3-CH ₂ COMe, 5-Br	102	90	a	101
3-CH ₂ COMe, 5-Cl	90	90	a	101
3-CH ₂ COMe, 5-Me	Liquid	85	a	101
3-CH ₂ COMe, 5-NO ₂	148	70	a	101

^a For simplicity, the many ketones prepared by reaction of a benzo[*b*]thienyl-magnesium bromide with a cyanoindane^{344, 478, 495, 501-503} are excluded from this table.

^b Methods: (a) Diethylethoxymagnesium malonate and an acid chloride; (b) nitrile and a Grignard reagent; (c) dimethylcadmium and an acid chloride; and (d) lithium acetate or lithium benzoate and a 2-benzo[*b*]thienyllithium.

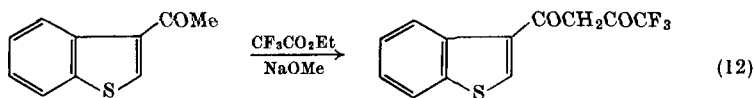
Several less widely used methods for preparing benzo[*b*]thienyl ketones will now be mentioned. A low yield of di(2-benzo[*b*]thienyl) ketone is obtained by treating 2-benzo[*b*]thienyllithium with *N,N*-dimethylcarbonyl chloride.⁶⁶⁷ The ketone (**284**) is prepared by

⁶⁶⁷ A. Cattaneo, G. Gelmi, and H. Zevio, *Farmaco (Pavia), Ed. Sci.* **16**, 741 (1961).



reaction of naphthalene-2,3-dicarboxylic anhydride with 3-benzo[*b*]-thienylmagnesium bromide.⁴⁷¹ The preparation of ketones from 2-benzo[*b*]thienylmethylmagnesium chloride and its 3-methyl derivative is discussed in Section VI, D, 4. 2-Acetyl-7-methylbenzo[*b*]thiophene may be obtained by oxidation of the corresponding alcohol.⁹⁰ 3-Benzo[*b*]thienylacetone may be prepared by reaction of the 3-carboxaldehyde with diazomethane⁶⁴³ (see Section VI, L, 1) or by heating 3-benzo[*b*]thienylacetic acid with sodium acetate and acetic anhydride.⁵⁵⁷

b. *General Properties.* Benzo[*b*]thienyl ketones form the usual (and other less common^{435, 668-671}) carbonyl derivatives; they are reduced to the corresponding alkylbenzo[*b*]thiophenes by the Clemmensen or Huang-Minlon methods^{81, 132, 135, 136, 139, 193, 281, 464, 614, 665}; and they undergo the Pfitzinger reaction with isatin.^{81, 132, 136, 193, 194, 436} 3-Ketones are less reactive than 2-ketones in these reactions,^{132, 464} and sterically hindered ketones may be inert.^{139, 637} Acylbenzo[*b*]thiophenes are converted into amides by the Willgerodt reaction, and acetyl compounds are oxidized to the corresponding carboxylic acid by hypohalite (Section VI, M). Ketones are reduced to alcohols by



lithium aluminum hydride^{465, 526} and react normally with Grignard reagents.⁴⁶⁵ 2- or 3-acetylbenzo[*b*]thiophene undergoes Claisen acylation with various fluoro esters [e.g., Eq. (12)]^{672, 673} to give the corresponding β -diketone, which will react with hydrazine to give a

⁶⁶⁸ F. L. Scott, M. Cashman, and J. Reilly, *J. Am. Chem. Soc.* **75**, 1510 (1953).

⁶⁶⁹ F. F. Blicke and E. L. Schumann, *J. Am. Chem. Soc.* **76**, 1228 (1954).

⁶⁷⁰ H. Zimmer, B. H. Gross, E. H. Gerlach, K. Fry, A. C. Pronay, and H. Schmank, *J. Org. Chem.* **24**, 1667 (1959).

⁶⁷¹ H. W. Zimmer, U.S. Patent 2,950,280 (1960); *Chem. Abstr.* **55**, 18665 (1961).

⁶⁷² L. B. Barkley and R. Levine, *J. Am. Chem. Soc.* **73**, 4625 (1951).

⁶⁷³ H. A. Wagner, U.S. Patent 3,200,128 (1965); *Chem. Abstr.* **63**, 13272 (1965).

pyrazole derivative.⁶⁷³ Acetylbenzo[*b*]thiophenes may be conveniently converted into the corresponding acetamido compounds by the Schmidt reaction with hydrazoic acid,^{76, 77, 102, 107} or by Beckmann rearrangement of the oxime.¹¹⁷ 2-Acetyl-3-methylbenzo[*b*]thiophene⁶⁷⁴ and a number of substituted 3-acetyl-^{144, 661} and 3-propionylbenzo[*b*]thiophenes⁶⁷⁵ undergo the Mannich reaction. The methyl group of acetylbenzo[*b*]thiophenes may be oxidized to the CHO group with selenium dioxide.^{107, 676} Baeyer–Villiger oxidation of 3-bromo- and 2,3-dibromo-6-acetylbenzo[*b*]thiophene gives in each case a mixture of the corresponding 1,1-dioxide and the 6-acetoxy-1,1-dioxide (Section VI, P, 2, *a*).¹⁰⁷

c. *Substitution in the Side Chain.* Bromoacetylbenzo[*b*]thiophenes are best prepared by treatment of the appropriate methyl ketone with bromine in carbon tetrachloride.^{218, 305, 336, 622, 623, 677} Small amounts of the ω,ω -dibromomethyl ketone are obtained in some cases,^{218, 622} but in all cases halogenation is confined to the side chain. Chloroacetylbenzo[*b*]thiophenes may be obtained analogously,^{678, 679} but they are more easily prepared by treatment of the methyl ketone with sulfuryl chloride.^{132, 464, 622} Bromoacetylbenzo[*b*]thiophenes have also been obtained by treatment of the appropriate diazomethyl ketone with hydrogen bromide in acetic acid.^{218, 557}

Hydrolysis of the hexamethylenetetramine salt of bromoacetylbenzo[*b*]thiophenes provides an efficient means of replacing the bromine atom by the amino group^{218, 337, 557, 680}; replacement by the dialkylamino group is effected by direct reaction of the bromoacetyl compound with a secondary amine.^{336, 622, 623} 3-Diazoacetyl-2-methylbenzo[*b*]thiophene undergoes the Wolff rearrangement in the presence of secondary amines to yield *N*-substituted 2-methylbenzo[*b*]thienyl-3-acetamides [Eq. (13)].⁵⁶⁸ Replacement of the halogen atom of haloacetylbenzo[*b*]thiophenes by a sulfur-containing group is discussed in Section VI, O, 1.

⁶⁷⁴ Laboratoria Pharmaceutica Dr. C. Janssen N.V. and N.V. Nederlandse Combinatie voor Chemische Industrie N.V., Belgian Patent 561,320 (1957); *Chem. Abstr.* **54**, 8855 (1960).

⁶⁷⁵ L. A. Gorum, Ph.D. Thesis, University of Mississippi (1967); *Dissertation Abstr.* **28B**, 2362 (1967).

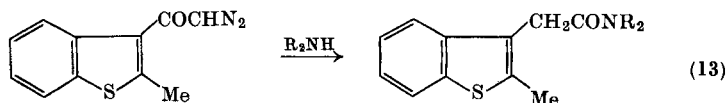
⁶⁷⁶ W. Ried and K. Sommer, *Ann. Chem.* **611**, 108 (1958).

⁶⁷⁷ V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res. (India)* **14B**, 11 (1955).

⁶⁷⁸ W. S. Emerson, U.S. Patent 2,673,856 (1954); *Chem. Abstr.* **49**, 1808 (1955).

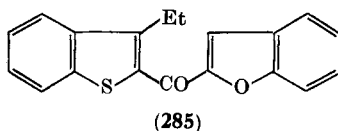
⁶⁷⁹ W. S. Emerson, *J. Am. Chem. Soc.* **73**, 1854 (1951).

⁶⁸⁰ E. D. Sych and E. D. Smaznaya-Il'ina, *Ukr. Khim. Zh.* **28**, 1087 (1962); *Chem. Abstr.* **60**, 10839 (1964).



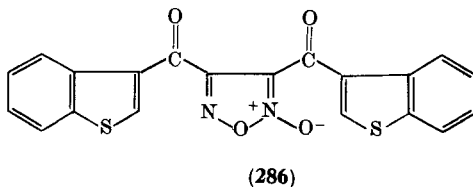
A chloroacetylbenzo[b]thiophene is readily converted into the corresponding benzo[b]thiophene carboxylic acid by alkaline hydrolysis of its pyridinium salt.^{132, 464}

2-Bromoacetylbenzo[b]thiophene is reduced to 2-(1,2-epoxyethyl)-benzo[b]thiophene by 1 mole of sodium borohydride in alkaline solution.³³⁶ 2-Chloroacetyl-3-ethylbenzo[b]thiophene and salicylaldehyde react together to give **285**.¹³² 2-Chloroacetyl-2,3-dihydrobenzo[b]thiophene is readily aromatized by potassium acetate to



2-acetylbenzo[b]thiophene, owing to the presence of a benzylic hydrogen atom in the β -position to the carbonyl group.⁶⁸¹

d. *Nuclear Substitution*. A claim⁴¹⁷ that nitration of 3-acetyl-, 3-propionyl-, and 3-butyrylbenzo[b]thiophene with fuming nitric acid in acetic acid and acetic anhydride at 0° gives solely the 2-nitro compound in each case, has been refuted.^{99, 654} Indeed, nitration of 3-acetylbenzo[b]thiophene under the above conditions has been shown to afford mainly 3-acetyl-4-nitrobenzo[b]thiophene, together with the 5-, 6-, and 7-nitro isomer and some 3-nitrobenzo[b]thiophene; no 3-acetyl-2-nitrobenzo[b]thiophene is obtained.⁹⁹

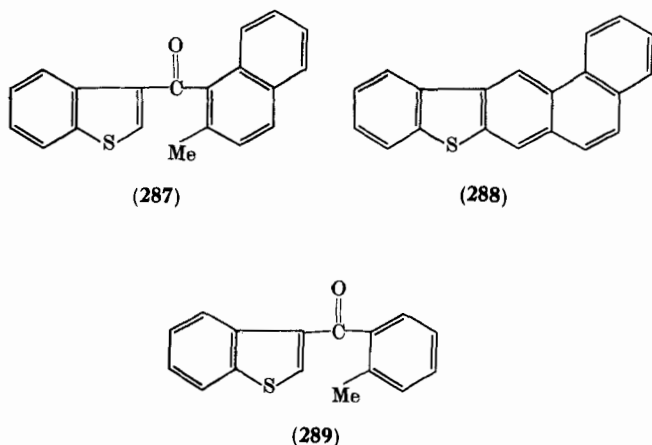


When the reaction is carried out in glacial acetic acid at reflux temperature, reaction takes place solely in the side chain to yield di(3-benzothiophenyl)furoxan (**286**).^{99, 654} Furoxans are also formed during the nitration of 3-acetyl-2-methyl-⁶⁵⁴ and 3-acetyl-2-methoxy-

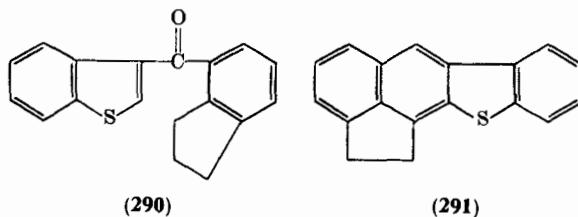
⁶⁸¹ V. Rosnati, G. Pagani, and F. Sannicolò, *Tetrahedron Letters* 1241 (1967).

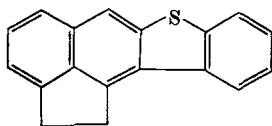
benzo[*b*]thiophene¹⁸³; the furoxan from the latter compound is formed at room temperature.

e. *Cyclization Reactions.* Elbs pyrolysis of suitable aroylbenzo[*b*]thiophenes has been used extensively as a source of polycyclic compounds containing a thiophene ring. The reaction may or may not proceed with rearrangement; 3-(2-methyl-1-naphthoyl)benzo[*b*]thiophene (**287**), for example, gives the expected product (**288**) on pyrolysis.⁶⁵⁷ 3-(2-Methylbenzoyl)benzo[*b*]thiophene (**289**), however, gives mainly the angular rearrangement product (**159**).⁶⁵⁸



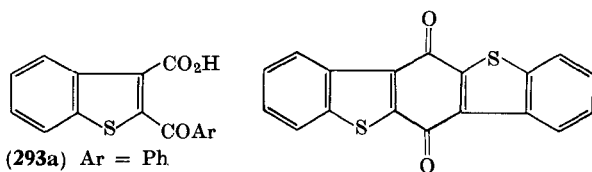
Isosteres of the carcinogenic hydrocarbon cholanthrene, in which ring C^{478, 501-503} or ring D^{344, 495} is replaced by a thiophene ring, have been prepared by Elbs pyrolysis of the appropriate indanoylbenzo[*b*]thiophene. For example, pyrolysis of the ketone (**290**) yields mainly the cholanthrene isostere (**291**), together with the rearrangement product (**292**).⁴⁷⁸ Such rearrangement products are often, but not always, obtained as by-products from Elbs pyrolysis of indanoylbenzo[*b*]thiophenes; it is not yet possible to decide a priori whether or not they will be formed.





(292)

Ketones (293a),⁶⁸² (293b),⁶⁷⁷ and (293c),⁶⁷⁷ prepared by interaction of benzo[*b*]thiophene-2,3-quinone and the appropriate ω -haloketone, are cyclized by benzoyl chloride and concentrated sulfuric acid to the

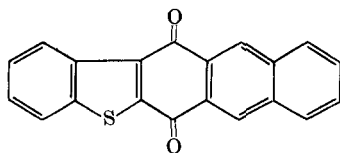


(293a) Ar = Ph

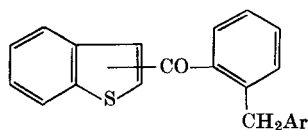
(293b) Ar = 2-Thienyl

(293c) Ar = 3-Benzo[*b*]thienyl

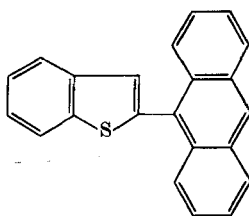
(294)



(295)



(296)



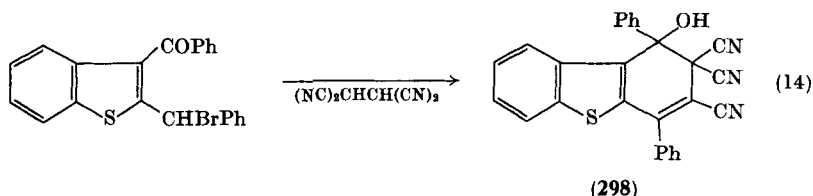
(297)

corresponding quinone (e.g., 294 from 293c). Cyclization of 284 with concentrated sulfuric acid yields the quinone (295).⁴⁷¹ 2- or 3-benzo[*b*]thienyl ketones of the type 296 (Ar = 1- or 2-naphthyl, or Ph) undergo cyclodehydration in acetic acid in the presence of hydrogen bromide to yield polycyclic compounds [e.g., 297 from 296 (2-benzo[*b*]

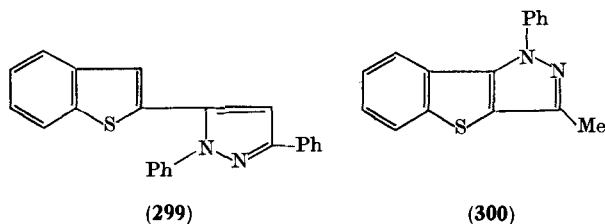
⁶⁸² B. D. Tilak, *Proc. Indian Acad. Sci.* **A33**, 131 (1951).

thienyl isomer, R = Ph)].⁵⁰⁴ The rates of cyclodehydration of the ketones (**296**) have been investigated in order to evaluate the relative significance of electronic and steric effects.⁶⁸³

f. *Miscellaneous Ketones and Reactions.* Reaction of 1,1,2,2-tetracyanoethane with the product of benzylic bromination of 2-benzyl-3-benzoylbenzo[*b*]thiophene in the presence of sodium hydride gives the tricyclic compound (**298**) [Eq. (14)].⁵¹⁹



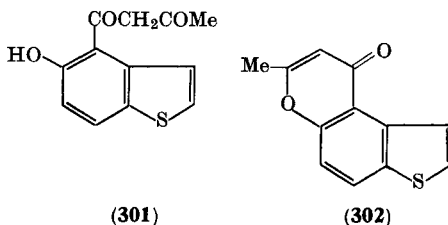
The phenylhydrazone of 2-benzo[*b*]thienylideneacetophenone readily cyclizes to 5-(2-benzo[*b*]thienyl)-1,3-diphenylpyrazoline (**299**).⁶⁴⁵



2-Acetyl-3-hydroxybenzo[*b*]thiophene, prepared by heating thio-salicylic acid with acetylacetone in the presence of sulfuric acid,¹⁴⁷ gives the pyrazole (**300**) on treatment with phenylhydrazine.⁶⁸⁴ 4-Acetyl-5-hydroxybenzo[*b*]thiophene, prepared by Fries rearrangement of 5-acetoxybenzo[*b*]thiophene,^{338, 340} yields the diketone (**301**) on Claisen acylation with ethyl acetate; with concentrated sulfuric acid **301** forms the thienochromone (**302**).³³⁸ The methyl group of 5-acetoxy-3-methylbenzo[*b*]thiophene causes steric congestion of the 4-position, and the acetyl group enters the 2-position on Fries rearrangement.³⁴⁰ Similarly, the acetyl group of 4-acetoxybenzo[*b*]thiophene enters the sterically more favorable 2- or 7-position.⁶¹⁴

⁶⁸³ P. D. Henson and F. A. Vingiello, *J. Org. Chem.* **32**, 3205 (1967).

⁶⁸⁴ W. J. Barry, I. L. Finar, and A. B. Simmonds, *J. Chem. Soc.* 4974 (1956).



M. CARBOXYLIC ACIDS

1. 2-Carboxylic Acids

The most widely used routes to benzo[b]thiophene-2-carboxylic acids are: (a) successive lithiation and carbonation of the parent benzo[b]thiophene,^{42, 76, 90, 98, 183, 477, 481, 487, 521, 685-687} (b) oxidation of the corresponding aldehyde,^{90, 91, 105, 189, 424, 477, 640} (c) hypohalite oxidation of the corresponding methyl ketone,^{82, 98, 189, 424} and (d) cyclization reactions (Section IV, D, and E). Acids prepared by these routes are listed in Table XV. Oxidation of aldehydes usually proceeds almost quantitatively with moist silver oxide,^{90, 91, 105, 189, 424} but potassium permanganate is satisfactory.^{477, 640}

Benzo[b]thiophene-2-carboxylic acids are less conveniently prepared by carbonation of the Grignard reagent formed from the corresponding 2-halobenzo[b]thiophene.^{189, 413, 424, 485, 487} The preparation of 2-carboxylic acids from 3-benzo[b]thienylmethylmagnesium chloride⁴⁸⁵ is discussed in Section VI, D, 4. The pyridinium salts of 2-chloroacetylbenzo[b]thiophene⁴⁶⁴ and its 3-ethyl derivative¹³² afford a good yield of the corresponding 2-carboxylic acid on treatment with aqueous sodium hydroxide.

Benzo[b]thiophene-2-carboxamides have been prepared by treatment of 2-benzo[b]thienyllithium with isocyanates,⁵⁶⁴ but are more conveniently obtained from the appropriate acid chloride by the conventional procedure.^{334, 481, 548, 556, 564, 686-688} The acid chlorides react with diazomethane to give the diazoketone,^{218, 689} and with dimethylcadmium^{76, 90} or diethyl ethoxymagnesium malonate^{218, 336}

⁶⁸⁵ S. Gronowitz, *Arkiv Kemi* **7**, 361 (1954-1955).

⁶⁸⁶ R. W. Goettsch, Ph.D. Thesis, University of Iowa (1957); *Dissertation Abstr.* **17**, 2831 (1957).

⁶⁸⁷ R. W. Goettsch and G. A. Wiese, *J. Am. Pharm. Assoc.* **47**, 319 (1958).

⁶⁸⁸ E. Campaigne and T. Bosin, *J. Med. Chem.* **10**, 945 (1967).

⁶⁸⁹ N. P. Kefford and J. M. Kelso, *Australian J. Biol. Sci.* **10**, 80 (1957).

TABLE XV
PREPARATION OF BENZO[b]THIOPHENE-2-CARBOXYLIC ACIDS

Substituents	Melting point (°C)	Yield (%)	Method ^a	Ref.
None	240–241	68, 20	d	339, 315
		62–80	a	685–687
		72, ?	b	91, 640
3-Me	244–246	65, 73	a	481, 521
		?	d	540
4-Me	197–198	64, 75	c, a	98
5-Me	218–219.5	73	a	98
6-Me	230–231	87, 79	c, a	98
7-Me	226	89	a	90
3,5-Me ₂	263–264	100	d	625
		83	c	82
3,7-Me ₂	238.5–239.5	86	c	82
5-OH, 3-Me	254–255	88	d	343
5-NH ₂ , 3-Me	267–268	?	d	331
5-NH ₂ , 3,6-Me ₂	271	90	d	330
5-NO ₂ , 3,6-Me ₂	312–313	80	d	330
6-SCH ₂ CO ₂ H	250	?	d	353
3-Me, 5-SCH ₂ CO ₂ H	274–275	?	d	332
3-Me, 5-SCH ₂ CH ₂ CO ₂ H	261–262	?	d	332
3-Br	274–275	59, 79	b, a	477
4-Br	272	55	d	344, 495
		96	b	105
5-Br	235	48	d	315
		68	a	76
6-Br	267	67	b	105
7-Br	288	55	b	105
3-Br, 7-Me	260–261	100	b	90
4-Br, 7-Me	253	100	b	90
6-Br, 7-Me	280	100	b	90
5-Cl, 3-Ph	263–265	16	d	349
5-NH ₂ , 3-Ph	219–220	?	d	333
5-NO ₂ , 3-Ph	250–251	?	d	185, 333
5,7-diNO ₂ , 3-Ph	252–253	?	d	334
5-NO ₂	237	45–70	d	218, 338, 422, 544, 545
3-Me, 5-NO ₂	303–305	90	d	298
3-OH, 7-NO ₂	160	?	d	494
3-OMe	176–177	94	a	183
5-OMe	215–216	40	d	341
6-OMe	251	7.5	d	341
		30	a	42

TABLE XV—*continued*

Substituents	Melting point (°C)	Yield (%)	Method ^a	Ref.
5,6-OMe ₂	260–261	11, 25	d	326, 339
4,5-OMe ₂	240–241	30	d	189
5,6,7-OMe ₃	180–181	37	d	341
6-OEt	221	70, 40	b, c	424
5,6-OEt ₂	245–246	31	d	341
5,6-OCH ₂ O-	295	98, 62	d	638, 189
		99, 80	b, c	189
5-CO ₂ H	> 310	63	a	76
4,5,6,7-F ₄	199–200	70	d	110
5,6,7-F ₃	242	40	d	110
4,5,7-F ₃	197–198	86	d	110
4,6,7-F ₃	204	70	d	110

^a Methods: (a) carbonation of the appropriate 2-benzo[*b*]thienyllithium; (b) oxidation of the corresponding aldehyde; (c) hypohalite oxidation of the corresponding methyl ketone; and (d) cyclization reaction.

to give the corresponding methyl ketone. The vinyl ester of benzo[*b*]thiophene-2-carboxylic acid has been prepared by reaction of the acid with vinyl acetate and mercuric sulfate^{690, 691}; dialkylamino^{692, 693} and alkyl^{90, 152, 497} esters have been prepared by the usual methods. Reduction of benzo[*b*]thiophene-2-(or 3)carboxylic acid with sodium amalgam yields the corresponding 2,3-dihydro compound.²¹²

Aminobenzo[*b*]thiophene-2-carboxylic acids are conveniently obtained by reduction of the corresponding nitro compound.^{152, 185, 333, 334, 336, 338, 497} Diazotization of these, followed by the usual replacement reactions of the diazonium group, provides many substituted benzo[*b*]thiophene-2-carboxylic acids, decarboxylation of which leads to some otherwise rather inaccessible benzo[*b*]thiophenes. 5-Hydroxybenzo[*b*]thiophene-2-carboxylic acid is most conveniently prepared from the corresponding amino compound by means of the Bucherer reaction,^{338, 497} in which the dicarboxylic acid (**303**) is formed as a by-product.¹⁵²

There is little reliable information on electrophilic substitution of

⁶⁹⁰ M. Hopff, *Bull. Soc. Chim. France* 1283 (1958).

⁶⁹¹ H. Lüsi, *Kunststoffe-Plastics* **3**, 156 (1956); *Chem. Abstr.* **52**, 11054 (1958).

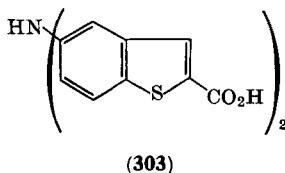
⁶⁹² W. Voegtli, U.S. Patent 2,857,383 (1958); *Chem. Abstr.* **53**, 6249 (1959).

⁶⁹³ W. Voegtli, U.S. Patent 2,876,235 (1959); *Chem. Abstr.* **53**, 20090 (1959).

TABLE XVI
BENZO[*b*]THIOPHENE 3-, 4-, 5-, 6-, AND 7-CARBOXYLIC ACIDS

Substituents	Melting point (°C)	Yield (%)	Method ^a	Ref.
3-CO ₂ H	176–177.5	55, 76	a	413, 476
		70, 87	b	91, 487
		?	c	695
		93	d	512, 513
2-Me, 3-CO ₂ H	194–195	50	a	481
		90	c	568
5-Me, 3-CO ₂ H	172–172.5	86	c	98
7-Me, 3-CO ₂ H	210–211	81, 100	b, a	78
		92	c	98
2,5-Me ₂ , 3-CO ₂ H	205–207	95	c	82
2-Ph, 3-CO ₂ H	188–189	87	d	483
2-Cyclohexyl, 3-CO ₂ H	211–212.5	19	d	483
2-(2-Naphthyl), 3-CO ₂ H	214	84, 27	d, a	54
5-OCH ₂ Ph, 3-CO ₂ H	224	48	a	337
5-Cl, 3-CO ₂ H	260–262	64, 50	b, c	144
5-Br, 3-CO ₂ H	284–285	60, 50	b, c	144
		60, 86	b, c	105, 76
6-Br, 3-CO ₂ H	199–200	67	b	105
7-Br, 3-CO ₂ H	271	72	b	105
4-CO ₂ H	190–191	50	d	294
		91	b	91
5-CO ₂ H	211–212	96	b	91
		55	a	315
		?	d	513, 557
6-CO ₂ H	216–217	82, 35	d	241, 294
		90	b	91
3-Br, 6-CO ₂ H	278–279.5	93	c	77
2,3-Br ₂ , 6-CO ₂ H	298–300	100	c	77
3-Br, 2-Me, 6-CO ₂ H	272–273	95	c	102
2-Br, 3-Me, 6-CO ₂ H	261–262	96	c	102
7-CO ₂ H	171–172	?	d	513
		91	b	91

^a Methods: (a) carbonation of the benzo[*b*]thienylmagnesium halide; (b) oxidation of the aldehyde; (c) hypohalite oxidation of the methyl ketone; and (d) hydrolysis of the nitrile.



benzo[*b*]thiophene-2-carboxylic acid. The mononitration mixture has not been separated, but the mixture of amines formed after successive decarboxylation and hydrodesulfurization contained *o*-aminoethylbenzene, thereby proving the presence of the 4-nitro isomer.⁴¹² Smaller quantities of *m*-aminoethylbenzene present in the mixture could have arisen from either the 5- or the 7-nitro isomer; the absence of the 3-isomer could not be proved conclusively. Monobromination, nitrosation, and nitration of 5-hydroxybenzo[*b*]thiophene-2-carboxylic acid, monobromination of 5-aminobenzo[*b*]thiophene-2-carboxylic acid, and mononitration of 5-acetamidobenzo[*b*]thiophene-2-carboxylic acid give the 4-substituted product in each case.^{152, 497}

Dibromination of 5-aminobenzo[*b*]thiophene-2-carboxylic acid affords the 4,6-dibromo compound.¹⁵² 5-Nitrobenzo[*b*]thiophene-2-carboxylic acid resists nitration at room temperature; at 100° decarboxylation takes place, and two unidentified trinitrobenzo[*b*]thiophenes have been isolated.¹⁵² Similarly, it is unaffected by bromine in refluxing acetic acid in the presence of sodium acetate; its sodium salt, however, readily gives the 3-bromo compound in aqueous solution.¹⁵² 3-Bromobenzo[*b*]thiophene-2-carboxylic acid may likewise be prepared from sodium benzo[*b*]thiophene-2-carboxylate.⁴⁷⁷ Dinitration of 5-bromobenzo[*b*]thiophene-2-carboxylic acid gives the 3,4-dinitro compound.⁶⁹⁴

2. 3-, 4-, 5-, 6-, and 7-Carboxylic Acids

These acids are generally prepared by (*a*) carbonation of the corresponding benzo[*b*]thienylmagnesium bromide^{54, 78, 315, 337, 476, 481} or iodide,^{87, 413} (*b*) oxidation of the corresponding aldehyde with moist silver oxide^{78, 91, 105, 487} or chromic acid,¹⁴⁴ (*c*) hypohalite oxidation of the corresponding methyl ketone,^{76, 77, 82, 98, 102, 144, 508, 695} or (*d*) hydrolysis of the appropriate nitrile^{54, 241, 483, 512, 513, 565} or the amide

⁶⁹⁴ O. Süss and M. Glos, German Patent 955,379 (1957); *Chem. Abstr.* **54**, 12848 (1960).

⁶⁹⁵ Smith, Kline & French Lab., British Patent 944,417 (1963); *Chem. Abstr.* **60**, 9282 (1964).

derived therefrom.^{81, 294, 557} Acids prepared by these routes are shown in Table XVI. 4-Bromobenzo[*b*]thiophene-3-carboxaldehyde could not be oxidized to the corresponding acid, presumably owing to steric interactions between the two large groups, which occupy positions corresponding to the *peri* positions in naphthalene.¹⁰⁵

Carbonation of the lithium derivative of 2-methoxybenzo[*b*]thiophene affords the corresponding 3-carboxylic acid.¹⁸³ 2-Methylbenzo[*b*]thiophene-3-carboxylic acid has been obtained (45%) by carbonation of 2-benzo[*b*]thienylmethylmagnesium chloride (Section VI, D, 4).⁵²⁸ *n*-Butyllithium reacts selectively with the bromine atom in 3-bromo-2-fluorobenzo[*b*]thiophene to give a product, which on carbonation affords 2-fluorobenzo[*b*]thiophene-3-carboxylic acid.⁴⁸² Benzo[*b*]thiophene-7-carboxylic acid is obtained by reduction of the corresponding thioindoxyl with amalgamated zinc and acetic acid.³¹⁵ Benzo[*b*]thiophene-3-carboxylic acid and its 2-ethyl derivative have been prepared in high yield by treatment of the pyridinium salt of the 3-chloroacetyl derivative with alkali.¹³²

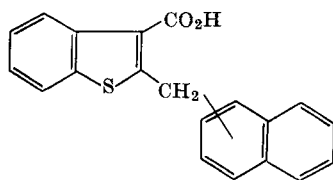
Esters, amides, and primary alcohols are obtained from benzo[*b*]thiophene carboxylic acids by standard procedures.^{337, 481, 565, 692, 693, 695} Acid chlorides undergo the Arndt-Eistert reaction,^{337, 568, 689} react with diethyl ethoxymagnesium malonate to give the corresponding methyl ketone,^{144, 557} and are reduced to the aldehyde with lithium tri-*tert*-butoxyaluminumhydride.³³⁷

Benzo[*b*]thiophene carboxylic acids have been decarboxylated by heating them with oxalic acid,²⁵⁴ by heating the ester with 1*N* NaOH in dioxane,⁴⁴¹ by heating the barium salt with barium hydroxide *in vacuo*,¹⁵² by heating them in quinoline with copper chromite^{347, 352, 353} or, preferably, with copper,^{109, 185, 189, 298, 315, 343, 344, 351, 412, 422, 638} and by heating them alone in quinoline⁵⁴ or pyridine.¹¹⁴

2-(1-Naphthoyl)- or 2-(2-naphthoyl)benzo[*b*]thiophene-3-carboxylic acid is reduced with zinc and sodium hydroxide to 2-(1-naphthylmethyl)- (**304a**) or 2-(2-naphthylmethyl)benzo[*b*]thiophene-3-carboxylic acid (**304b**), respectively.⁶⁹⁶ Heating either with zinc dust and zinc chloride gives the corresponding benzophenanthrenethiophene, e.g., **305** from **304a**.⁶⁹⁶

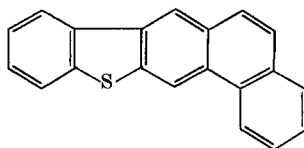
Van Zyl *et al.*⁴¹² have shown that mononitration of benzo[*b*]thiophene-3-carboxylic acid gives mainly the 4-nitro compound, together with the 5- or 7-, and 6-isomers. Martin-Smith and Armstrong⁹⁹

⁶⁹⁶ G. N. Pillai, T. S. Murthy, and B. D. Tilak, *Indian J. Chem.* **1**, 112 (1963).



(304a) 1-Naphthyl

(304b) 2-Naphthyl



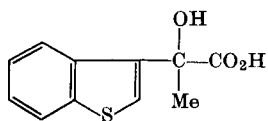
(305)

recently confirmed these observations, and conclusively identified the 7-isomer; they also obtained 3-nitrobenzo[*b*]thiophene. Methyl benzo[*b*]thiophene-6-carboxylate is brominated predominantly in the 3-position.⁷⁷

3. Acetic Acids

These are usually prepared by the following methods: (a) the Willgerodt reaction on the corresponding methyl ketone,^{82, 98, 337, 485, 557} (b) hydrolysis of the corresponding cyanomethyl compound,^{77, 337, 485, 499, 517, 521, 568} (c) cyclization reactions (Section IV, C) (for 3-acetic acids only),^{143, 299, 310, 311, 313, 351} or (d) the Arndt-Eistert reaction on the corresponding carbonyl chloride, which may lead directly to the acetic acid⁶⁸⁹ or its amide.^{337, 568}

Carbonylation of benzo[*b*]thienylmethylmagnesium chlorides usually gives only a low yield of the required acetic acid (Section VI, D, 4).^{485, 517, 526, 528} α -Hydroxy- α -(3-benzo[*b*]thienyl)propionic acid (306) is formed by hydrolysis of the product of the reaction between 3-benzo[*b*]thienylmagnesium bromide and ethyl pyruvate.²⁰⁷



(306)

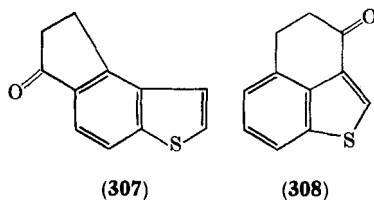
3-Benzo[*b*]thienylacetic acid and its 6-ethoxy derivative are obtained in low yield from the corresponding thioindoxyl by the Reformatsky reaction with ethyl bromoacetate.⁵⁶⁹ 4-Benzo[*b*]thienylacetic acid is obtained by successive dehydrogenation and hydrolysis of the ester mixture shown in Eq. (10).^{355, 448} 7-Benzo[*b*]thienylacetic acid may be prepared similarly.³⁶³

Amides^{143, 311, 568, 569} and esters^{143, 692} of benzo[*b*]thienylacetic acids are prepared by the usual methods.

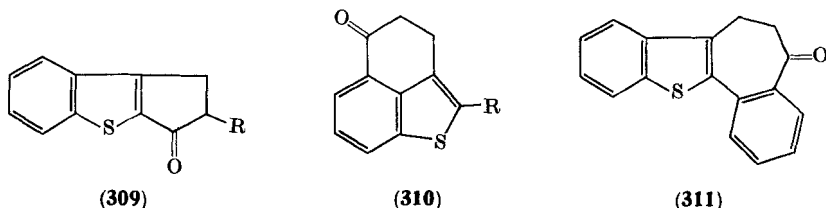
4. β -(Benzo[b]thienyl)propionic Acids

Benzo[b]thiophene-2-,^{76, 90, 93, 165, 183, 477, 520} 3-,^{78, 144, 183, 477, 487, 520, 697} and 6-carboxaldehydes⁷⁷ smoothly undergo the Doebner reaction with malonic acid to give the corresponding β -(benzo[b]thienyl)acrylic acid, which can be reduced to the β -(benzo[b]thienyl)propionic acid, either catalytically,^{144, 477} or with sodium amalgam in aqueous sodium carbonate.^{76, 77, 90} β -(Benzo[b]thienyl)propionic acids may be obtained also from the corresponding halomethylbenzo[b]thiophene by the conventional diethyl malonate synthesis,^{447, 490, 499, 535, 536} or by reaction of a β -(benzo[b]thienyl)ethyl halide with potassium cyanide, followed by hydrolysis of the product.⁴⁴⁷ They have also been prepared by cyclization reactions (Section IV, F),^{347, 351, 618} by the Willgerodt reaction of the corresponding ethyl ketone,⁴⁸⁵ and by the Arndt-Eistert reaction on the corresponding acetic acid.^{313, 351}

β -(4-Benzo[b]thienyl)propionic acid is obtained by dehydrogenation of the spirolactone (**144**); it undergoes cyclization in the presence of liquid hydrogen fluoride to give the isomeric ketones (**307** and **308**).⁴⁴⁷ β -(3-Benzo[b]thienyl)propionyl chloride and its α -methyl derivative



undergo Friedel-Crafts cyclization in the 2-position to yield the ketones (**309**; R = H or Me).⁴⁹⁹ If the 2-position is blocked by Me or Ph, cyclization usually takes place in the 4-position to give the ketones

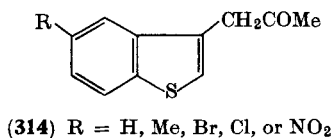
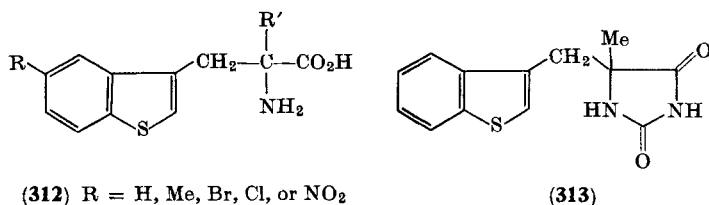


(**310**; R = Me or Ph).⁴⁴⁷ Cyclization of β -(2-bromo-3-benzo[b]thienyl)propionic acid with liquid hydrogen fluoride, however, proceeds with

⁶⁹⁷ N. V. Bac, N. P. Buu-Hoi, and N. D. Xuong, *Bull. Soc. Chim. France* 1077 (1962).

expulsion of the bromine atom to give **309** ($R = H$); cyclization of the acid chloride with aluminum chloride gives mainly **310** ($R = Br$).⁴⁴⁷ Cyclization of β -(2-phenyl-3-benzo[*b*]thienyl) propionic acid yields, in addition to **310** ($R = Ph$), the ketone (**311**), formed by cyclization into the benzene ring.⁴⁴⁷

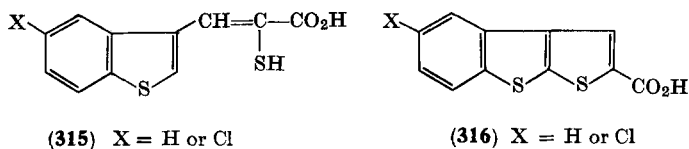
The azlactone formed from benzo[*b*]thiophene-2-carboxaldehyde and hippuric acid reacts with hydriodic acid and red phosphorus to give α -amino- β -(2-benzo[*b*]thienyl)propionic acid, and with sodium hydroxide to give α -benzamido- β -(2-benzo[*b*]thienyl)acrylic acid.⁴⁷⁷ A series of α -amino- β -(5-substituted-3-benzo[*b*]thienyl)propionic acids (**312**; $R' = H$) has been prepared by hydrolysis of the product of



the reaction between the appropriate 3-halomethyl compound and diethyl sodioacetamidomalonate.¹⁰¹

Alkaline hydrolysis of the hydantoins (**313**), prepared by the standard procedure from the corresponding ketones (**314**), gives a good yield of the α -substituted- α -amino acids (**312**; $R' = Me$).¹⁰¹

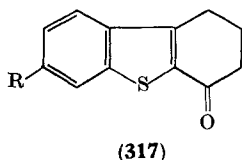
β -Amino- β -(2- or 3-benzo[*b*]thienyl)propionic acid may be prepared by treatment of the corresponding aldehyde with malonic acid in the presence of acetic acid and ammonium acetate; the corresponding acrylic acid is formed as a by-product in each case.⁵²⁰



The β -(3-benzo[*b*]thienyl)- α -mercaptoacrylic acids (**315**), prepared by hydrolysis of the corresponding 5-(3-benzo[*b*]thienylidene)-rhodanine, may be cyclized by iodine in tetrahydrofuran to give the tricyclic compounds (**316**).⁶⁴⁸

5. α -Benzo[*b*]thiophenealkane- ω -carboxylic Acids

Friedel-Crafts acylation of benzo[*b*]thiophene and its derivatives with succinic anhydride^{132, 439, 662, 663} or the ester chloride of succinic acid^{614, 618, 659, 662} gives a γ -keto acid (or ester), which is reduced to the corresponding γ -(benzo[*b*]thienyl)butyric acid by the Huang-Minlon or Clemmensen method. γ -(Benzo[*b*]thienyl)butyric acids may alternatively be prepared by the diethyl malonate synthesis on the appropriate halide,^{439, 499} by the Arndt-Eistert reaction on the corresponding propionyl chloride,^{499, 618} or by cyclization.^{347, 618} The ketones (**317**; R = H or OMe)³⁴⁷ have been prepared by cyclization



of the appropriate γ -(3-benzo[*b*]thienyl)butyric acid or acid chloride.^{439, 499, 618, 659} If, however, the 2-position is occupied by an ethyl group, the ketone (**310**; R = Et) is obtained.^{662, 663} Cyclization of γ -(5-benzo[*b*]thienyl)butyric acid (prepared by dehydrogenation of the methyl ester of its 2,3-dihydro derivative) yields two isomeric ketones, formed by cyclization into the 4- and 6-position, respectively; the former predominates.⁴²⁶

δ -(Benzo[*b*]thienyl)valeric acids may be prepared and cyclized by methods analogous to those described above.^{347, 500}

Friedel-Crafts reaction of benzo[*b*]thiophene with ester chlorides of the type $\text{EtO}_2\text{C}(\text{CH}_2)_n\text{COCl}$ ($n = 4-8$) gives a mixture of the corresponding 2- and 3-keto ester.¹³⁵ The 3-isomers may also be obtained by reaction of di(3-benzo[*b*]thienyl)cadmium with the above ester chlorides.¹³⁵

6. Dicarboxylic Acids

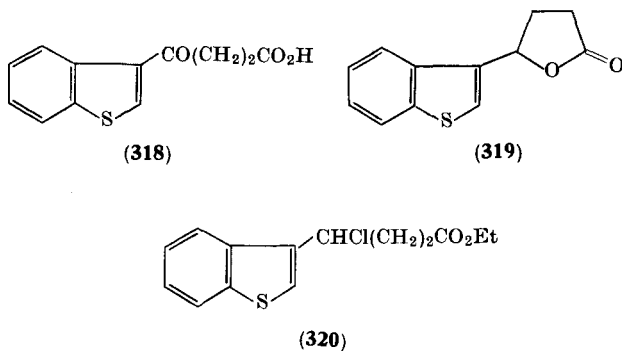
Benzo[*b*]thiophene-2,3-dicarboxylic acid may be prepared by carbonation of the product from the reaction of either 3-bromo- or

2,3-dibromobenzo[*b*]thiophene with an excess of *n*-butyllithium (50% yield),⁵¹¹ by successive treatment of benzo[*b*]thiophene-3-carboxylic acid with ethyl iodide and magnesium, and carbon dioxide (10% yield),³¹⁵ and by oxidation of 2-methylbenzo[*b*]thiophene-3-carboxylic acid.⁵²⁸ Successive treatment of 5-bromobenzo[*b*]thiophene with an excess of *n*-butyllithium and carbon dioxide gives benzo[*b*]thiophene-2,5-dicarboxylic acid.⁷⁶ Carbonation of the di(bromo-magnesium)derivative of 3,5-dibromobenzo[*b*]thiophene affords the 3,5-dicarboxylic acid.⁷⁶ Benzo[*b*]thiophene-4,5-dicarboxylic acid may be obtained by dehydrogenation of the corresponding 4,5,6,7-tetrahydro compound.^{361, 367}

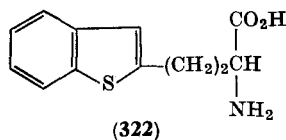
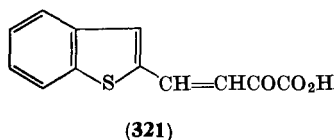
Benzo[*b*]thiophene-2,3-dicarboxylic anhydride reacts with phenol and resorcinol, respectively, to yield the benzo[*b*]thiophene analogs of phenolphthalein and fluorescein.⁶²⁵

7. Miscellaneous Carboxylic Acids

Borohydride reduction of the keto acid (**318**) yields the lactone (**319**), which is converted into the γ -chloro ester (**320**) by successive treatment with thionyl chloride and ethanol. Treatment of **320** with potassium *tert*-butoxide yields the *trans* ester (**203**; R = CO₂Et).^{466, 620}



Reaction of benzo[*b*]thiophene-2-carboxaldehyde with pyruvic acid yields the keto acid (**321**), the oxime of which gives α -amino- γ -(2-benzo[*b*]thienyl)butyric acid (**322**) on catalytic hydrogenation, and β -(2-benzo[*b*]thienyl)acrylonitrile on treatment with acetic anhydride; the latter yields β -(2-benzo[*b*]thienyl)acrylic acid on hydrolysis.⁶⁴⁶



2-Benzo[b]thienylmagnesium bromide is said to react with dialkyl oxalates at 36–40° to give esters of 2-benzo[b]thienylglyoxalic acid, and at 110–115° to give esters of 2-benzo[b]thienylglycolic acid.⁶⁹⁸

N. SULFONIC ACIDS

1. Preparation

There is surprisingly little reliable information on the sulfonation of benzo[b]thiophene or its derivatives. Benzo[b]thiophene is more readily sulfonated than naphthalene.⁶⁹⁹ Reaction with concentrated sulfuric acid at 80° gives a mixture of mono-, di-, and trisulfonic acids, reaction with 70% sulfuric acid at 80° gives a monosulfonic acid,⁶⁹⁹ and reaction with 18% oleum gives a disulfonic acid⁸⁶; in each case the orientation of the products is unknown. Treatment of benzo[b]thiophene with concentrated sulfuric acid in acetic anhydride at 20° gives 3-acetylbenzo[b]thiophene (*ca.* 10%) and a sulfonation product (isolated as the potassium salt), which was believed to be the 3-sulfonic acid.⁶⁶⁰ Recently, the sulfonation product has been shown to contain the 2- (8%) and 3-isomer (92%), by conversion into the sulfonyl chlorides and reduction to a separable mixture of 2- and 3-mercaptobenzo[b]thiophene.⁸⁴

Sulfonation⁶⁶⁰ or chlorosulfonation⁵⁰⁷ of 2- or 3-methylbenzo[b]thiophene takes place in the free thiophene position. Sulfonation of 5-methylbenzo[b]thiophene takes place in the thiophene ring, but more precise information is not available.⁶⁶⁰ Similarly, it is uncertain whether sulfonation of 2,3-dimethylbenzo[b]thiophene occurs in the 5- or 6-position.⁶⁶⁰

Potassium benzo[b]thiophene-4-sulfonate may be prepared by treating 4-mercaptobenzo[b]thiophene in dimethylformamide with oxygen in the presence of potassium hydroxide. It gives a disulfonic acid of undetermined structure on further sulfonation.⁸⁶

⁶⁹⁸ I. I. Lapkin and Yu. P. Dormidontov, *Uch. Zap., Permsk. Gos. Univ.* **141**, 289 (1966); *Chem. Abstr.* **68**, 114334 (1968).

⁶⁹⁹ P. N. Gorelov, *Pererabotka, Vydelenie, i Analizy Koksokhim. Produktov Sb.* **17** (1961); *Chem. Abstr.* **59**, 11398 (1963).

Sulfonation of 4-nitrobenzo[b]thiophene gives the 3-sulfonic acid in low yield.⁸⁴ Sulfonation of 3-nitro- and 3-bromo-2-nitrobenzo[b]thiophene gives in each case a monosulfonic acid of undetermined structure.⁶⁹⁴

2. Properties

Benzo[b]thiophene sulfonic acids (isolated as the potassium salts) may be converted into the sulfonyl chloride, and then into the corresponding sulfonamide,⁶⁶⁰ sulfanilide,⁶⁶⁰ sulfonate ester,⁸⁶ or thiol.⁸⁴ Sulfonyl chlorides are hydrolyzed by boiling water to the corresponding sulfonic acid.⁶⁶⁰

Desulfonation is slower than with naphthalene sulfonic acids.⁴⁶ It is accomplished by heating the calcium salt with superheated steam in the presence of 85% phosphoric acid,⁶⁶⁰ or by heating the potassium salt with superheated steam in the presence of sulfuric acid.⁸⁴

Nitration of the sulfonation product of benzo[b]thiophene, followed by desulfonation of the resulting products, gives a mixture of nitrobenzo[b]thiophenes, the composition of which depends on the nitration conditions (Section VI, E, 1).⁸⁴

O. DERIVATIVES WITH SULFUR IN A SIDE CHAIN

1. Mercaptobenzo[b]thiophenes, Sulfides, and Disulfides

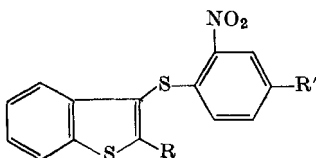
2-Mercaptobenzo[b]thiophene^{506, 507, 700} and its 3-methyl and 3,5- and 3,7-dimethyl derivatives⁵⁰⁶ are conveniently prepared by successive treatment of the appropriate 2-benzo[b]thienyllithium with sulfur and acid; 3-mercaptobenzo[b]thiophene^{84, 505-507} and its 2-methyl derivative⁵⁰⁷ may be prepared similarly from an appropriate 3-benzo[b]thienylmagnesium halide. Any disulfide by-products may be reduced to the mercaptans.^{505, 506} 2-Mercaptobenzo[b]thiophene may also be synthesized by acidic hydrolysis of the product obtained by treating 2-benzo[b]thienyllithium with 2-methylthiirane (propylene sulfide).⁷⁰¹ 3-Mercaptobenzo[b]thiophene containing 8% of its 2-isomer may be prepared by reduction of the corresponding sulfonyl chloride with zinc and acid,⁸⁴ and 3-mercapto-2-methyl- and 2-mercapto-3-methylbenzo[b]thiophene may be prepared similarly using lithium aluminum hydride.⁵⁰⁷ Successive treatment of 2-benzo-

⁷⁰⁰ R. B. Mitra, L. J. Pandya, and B. D. Tilak, *J. Sci. Ind. Res. (India)* **16B**, 348 (1957).

⁷⁰¹ R. D. Schuetz and W. L. Fredericks, *J. Org. Chem.* **27**, 1301 (1962).

[*b*]thienyllithium with sulfur and ethyl iodide gives 2-ethylmercaptobenzo[*b*]thiophene (2-benzo[*b*]thienyl ethyl sulfide).⁶³⁹ 2-Phenylmercaptobenzo[*b*]thiophene (2-benzo[*b*]thienyl phenyl sulfide) may be prepared by deamination of 2-benzo[*b*]thienyl 2-aminophenyl sulfide (see below), or by treating 2-benzo[*b*]thienyllithium with diphenyl disulfide.⁷⁰⁰ 5-Phenylmercapto-3-phenylbenzo[*b*]thiophene is a by-product of the cyclodehydration of phenacyl phenyl sulfide (Section IV, C)²⁹⁹ and 2-^{300, 702} and 3-(*p*-tolylmercapto)-5-methylbenzo[*b*]thiophene^{702, 703} may be prepared by ring-closure reactions (Sections IV, B and C).

Mercaptobenzo[*b*]thiophenes are readily characterized through the formation of benzo[*b*]thienyl 2,4-dinitrophenyl sulfides by reaction with 2,4-dinitrochlorobenzene in the presence of base. 2-^{506, 700} and 3-mercaptobenzo[*b*]thiophene⁵⁰⁵ are readily oxidized to the corresponding disulfides (e.g., with nitric acid).



(**323a**) R = Me, R' = NO₂

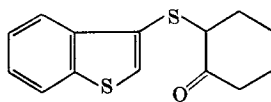
(**323b**) R = R' = H

A Friedel-Crafts reaction between 2-methylbenzo[*b*]thiophene and 2,4-dinitrobenzenesulfonyl chloride affords the sulfide (**323a**), which gives 3-mercapto-2-methylbenzo[*b*]thiophene and 2,4-dinitroanisole on treatment with methanolic potassium hydroxide.⁷⁰¹ A similar reaction between benzo[*b*]thiophene and 2,4-dinitrobenzenesulfonyl chloride affords a mixture of 2- and 3-benzo[*b*]thienyl 2,4-dinitrophenyl sulfide,⁷⁰¹ whereas it is reported that benzo[*b*]thiophene and 2-nitrobenzenesulfonyl chloride give only 3-benzo[*b*]thienyl 2-nitrophenyl sulfide (**323b**), together with 2,2'-dinitrodiphenyl disulfide and 2,2'-dibenzo[*b*]thienyl.⁵⁰⁵ Sulfide **323b** may be prepared also by treating 3-mercaptobenzo[*b*]thiophene with 2-nitrochlorobenzene in the presence of base.⁵⁰⁵ Reduction of **323b**, followed by diazotization of the resulting amine and cyclization of the diazonium salt by heating it in boiling 50% sulfuric acid (Pschorr-type synthesis) gives benzo[*b*]-

⁷⁰² V. Prey, U.S. Patent 2,949,471 (1960); *Chem. Abstr.* **55**, 2686 (1961).

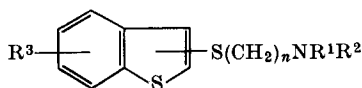
⁷⁰³ V. Prey, Austrian Patent 195,422 (1958); *Chem. Abstr.* **52**, 9216 (1958).

thiopheno[3,2-*b*]benzo[*b*]thiophene (**154**).⁵⁰⁵ Compound **153** may be prepared similarly.⁷⁰⁰ An attempt to synthesize **153** by cyclization of 2-phenylmercaptobenzo[*b*]thiophene with phenylsodium was unsuccessful; part of the sulfide was recovered and the rest was cleaved to benzo[*b*]thiophene.⁷⁰⁰



(324)

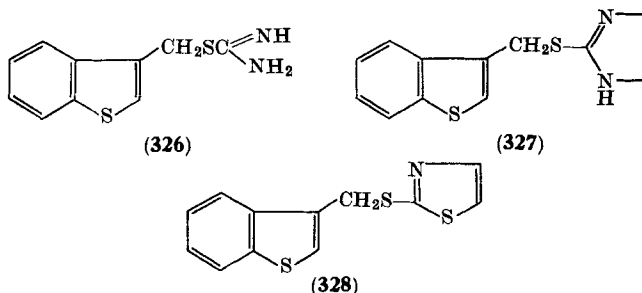
3-Mercaptobenzo[*b*]thiophene condenses with 2-bromocyclohexanone in aqueous sodium hydroxide to give **324**, which is cyclized by phosphorus pentoxide in boiling benzene to give 1,2,3,4-tetrahydrobenzo[*b*]thiopheno[3,2-*b*]benzo[*b*]thiophene,⁵⁰⁵ dehydrogenation of which gives **154**.⁵⁰⁵ Mitra *et al.*⁷⁰⁰ have synthesized **153** similarly. Condensation of 2-mercaptobenzo[*b*]thiophene with bromoacetaldehyde dimethyl acetal followed by cyclization of the resulting 2-benzo[*b*]thienyl 2,2-dimethoxyethyl sulfide with PPA affords thieno[2,3-*b*]benzo[*b*]thiophene (**250**; R = H).⁷⁰⁰ 3-Phenylthieno[2,3-*b*]benzo[*b*]thiophene (**250**; R = Ph) may be synthesized by cyclization of 2-benzo[*b*]thienyl phenacyl sulfide with phosphorus pentoxide.⁴⁶⁷ 3-Phenylthieno[3,2-*b*]benzo[*b*]thiophene may be prepared similarly.⁴⁶⁷



(325)

Schuetz and Heyd^{506, 507} have prepared several compounds with the general formula (325) by treating 2-mercaptobenzo[*b*]thiophene, its 3-methyl, 3,5- or 3,7-dimethyl derivative, or 3-mercaptobenzo[*b*]thiophene, with various haloalkylamines.

4-Mercaptobenzo[*b*]thiophene is readily oxidized in the presence of potassium hydroxide to give potassium benzo[*b*]thiophene-4-sulfonate.⁸⁶ It reacts with *S*-*n*-propylmethylphosphonochloridothioate in the presence of triethylamine to give *S*-(4-benzo[*b*]thienyl)-*S*-*n*-propylmethylphosphonodithioate (**240**; X = S, R = H) which exhibits pesticidal activity.⁶¹²



3-Chloromethylbenzo[*b*]thiophene reacts with thiourea,^{704, 705} ethylene thiourea (2-mercapto-2-imidazoline),⁷⁰⁵ and 2-mercaptothiazole⁵²¹ to give *S*-(3-benzo[*b*]thienyl)methylthiourea (326), 2-(3-benzo[*b*]thienyl)methylmercapto-2-imidazoline (327), and 2-(3-benzo[*b*]thienyl)methylmercaptothiazole (328), respectively. 2-Chloromethyl- and 2,3-di(chloromethyl)benzo[*b*]thiophene react similarly with thiourea and ethylene thiourea to give the 2- and 2,3-disubstituted analogs of 326 and 327, respectively.⁷⁰⁵ 3-Mercapto-methylbenzo[*b*]thiophene may be prepared by treating 326 with sodium hydroxide⁷⁰⁴; it affords a disulfide on treatment with iodine.⁷⁰⁶ 3-Bromo- or 3-chloroacetylbenzo[*b*]thiophene react with sodium sulfide to give di(3-benzo[*b*]thenoyl) sulfide,^{679, 707, 708} and 2- or 3-bromoacetylbenzo[*b*]thiophene react with sodium thiophenoxide to give 2- or 3-benzo[*b*]thenoyl phenyl sulfide.³⁰⁵ Treating 3-chloroacetylbenzo[*b*]thiophene with ammonium dithiocarbamate yields mainly 4-(3-benzo[*b*]thienyl)-2-thiazolyl disulfide (329),^{679, 707} which is reduced to 4-(3-benzo[*b*]thienyl)-2-mercaptothiazole by zinc and acid.^{679, 707, 709} A reaction in which the ammonium dithiocarbamate used was of "poor quality" gave di(3-benzo[*b*]thenoyl) sulfide as a major product.^{679, 707}

⁷⁰⁴ L. Nutting, R. M. Silverstein, and C. M. Himel, U.S. Patent 3,041,351 (1962); *Chem. Abstr.* **57**, 13729 (1962).

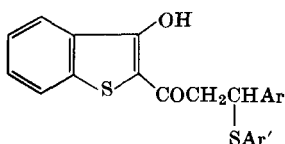
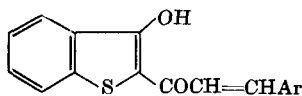
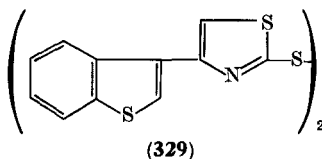
⁷⁰⁵ J. A. Lambrech and W. H. Henesley, British Patent 889,002 (1962); *Chem. Abstr.* **57**, 4635 (1962); U.S. Patent 3,186,990 (1965); *Chem. Abstr.* **63**, 7018 (1965).

⁷⁰⁶ L. Nutting, R. M. Silverstein, and C. M. Himel, U.S. Patent 3,033,875 (1962); *Chem. Abstr.* **57**, 12438 (1962).

⁷⁰⁷ W. S. Emerson and T. M. Patrick, U.S. Patent 2,612,504 (1952); *Chem. Abstr.* **47**, 7549 (1953).

⁷⁰⁸ W. S. Emerson, U.S. Patent 2,620,344 (1952); *Chem. Abstr.* **47**, 10556 (1953).

⁷⁰⁹ W. S. Emerson and T. M. Patrick, U.S. Patent 2,610,189 (1952); *Chem. Abstr.* **47**, 4121 (1953).

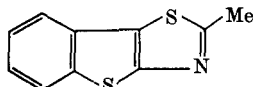
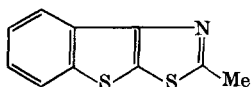


Base-catalyzed condensation of 2-(acetyl)thioindoxyl with aromatic aldehydes affords compounds with the general formula **330**, which give the adducts **331** with aryl mercaptans in the presence of piperidine.⁵⁸²

2. Miscellaneous Compounds

3-Thiocyanomethylbenzo[*b*]thiophene may be prepared by treating 3-chloromethylbenzo[*b*]thiophene with potassium thiocyanate.^{473, 710}

3-Chloroacetylbenzo[*b*]thiophene and its alkyl derivatives react with thiourea to give the corresponding 5-(3-benzo[*b*]thienyl)-2-aminothiazole.¹³² 3-Acetamidoacetylbenzo[*b*]thiophene affords 2-methyl-5-(3-benzo[*b*]thienyl)thiazole on treatment with phosphorus



pentasulfide.⁶⁸⁰ Treatment of 3-thioacetamidobenzo[*b*]thiophene (Section VI, F) with alkaline potassium ferricyanide affords 2-methyl-[1]benzthieno[3,2-*d*]thiazole (**332**).⁵⁵¹ The latter compound may be prepared also from 2-bromo-3-thioacetamidobenzo[*b*]thiophene by treating it with cuprous cyanide in pyridine⁵⁵² or by steam distillation.^{551, 552} When 2-(acetamido)thioindoxyl is fused with phosphorus pentasulfide, the isomer **333** of **332** is obtained.⁷¹¹

⁷¹⁰ A. H. Schlesinger and D. T. Mowry, U.S. Patent 2,572,574 (1951); *Chem. Abstr.* **46**, 2231 (1952).

⁷¹¹ Z. I. Miroshnichenko and M. A. Al'perovich, *Zh. Obshch. Khim.* **32**, 612 (1962); *Chem. Abstr.* **58**, 2441 (1963).

P. BENZO[b]THIOPHENE-1-OXIDES AND -1,1-DIOXIDES

1. *Benzo[b]thiophene-1-oxides*

These compounds are known only as their 2,3-dihydro derivatives. Oxidation of 2,3-dihydrobenzo[b]thiophene-3-carboxylic acid with dinitrogen tetroxide affords a mixture of *cis*- (**25**) (80%) and *trans*-2,3-dihydrobenzo[b]thiophene-3-carboxylic acid 1-oxide (20%).²²¹ In contrast, oxidation with methanolic sodium periodate gives exclusively, and with methanolic hydrogen peroxide predominantly, the *trans* isomer. The parent acid cannot be oxidized to the 1,1-dioxide with hydrogen peroxide; it has been suggested that the initially formed *trans*-1-oxide is sterically hindered. In support of this, the *cis*-1-oxide is readily oxidized with hydrogen peroxide to the 1,1-dioxide. The parent acid may be oxidized readily to the 1,1-dioxide with potassium permanganate. 2-*d*-2-Methyl-2,3-dihydrobenzo[b]thiophene similarly affords a mixture of the diastereomeric 1-oxides (**20** and **21**) with peracetic acid (see also Section III, D, 1).²¹⁷ With *tert*-butyl hydroperoxide 2,3-dihydrobenzo[b]thiophene affords the 1-oxide⁷¹² whereas, with peracetic acid, it gives the 1,1-dioxide.^{426, 713}

Acids catalyze the rearrangement of *cis*-2,3-dihydrobenzo[b]thiophene-3-carboxylic acid 1-oxide (**25**) to the more stable *trans* isomer.²²¹ Both isomers eliminate water on treatment with an excess of hydrochloric acid, or on pyrolysis, to give benzo[b]thiophene-3-carboxylic acid.²²¹ On treatment with acetic anhydride at 100°, 2- and 3-methyl- and 2,5- and 2,7-dimethyl-2,3-dihydrobenzo[b]thiophene-1-oxide also eliminate water to give the corresponding benzo[b]thiophene.²⁸⁰

2. *Benzo[b]thiophene-1,1-dioxides*

a. *General Methods of Preparation.* The synthesis of benzo[b]thiophene-1,1-dioxides by ring closure is discussed in Section IV. They are commonly prepared by peracid oxidation of benzo[b]thiophenes. Peracetic acid is the usual reagent, but perbenzoic,⁷¹⁴ permaleic,⁷¹⁵ and trifluoroperacetic¹⁰⁷ acid also have limited value. Though

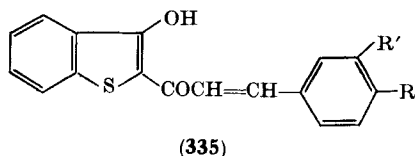
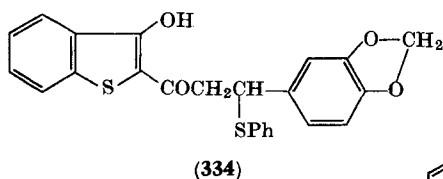
⁷¹² S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Inst. Petrol.* **40**, 76 (1954).

⁷¹³ J. F. Ford and V. O. Young, *Am. Chem. Soc., Div. Petrol. Chem., Preprints* **10**, C-111 (1965).

⁷¹⁴ A. Greco, G. Modeno, and P. E. Todesco, *Gazz. Chim. Ital.* **90**, 671 (1960).

⁷¹⁵ R. Kavčič and B. Plesničar, *Bull. Sci., Conseil Acad. RSF Yougoslavie* **10**, 177 (1965); *Chem. Abstr.* **64**, 674 (1966).

dibenzothiophene affords a sulfone with *tert*-butyl hydroperoxide, benzo[*b*]thiophene does not react.⁷¹³ Oxidation of benzo[*b*]thiophene derivatives to 1,1-dioxides is sometimes complicated by the ability of the products to undergo self-condensation (Section VI, P, 2, *d*). When treated with an equimolar amount of trifluoroperacetic acid, 6-acetyl-3-bromobenzo[*b*]thiophene gives the sulfone in quantitative yield.¹⁰⁷ Under identical conditions 6-acetyl-2,3-dibromobenzo[*b*]thiophene affords a mixture of starting material, the sulfone, and 6-acetoxy-2,3-dibromobenzo[*b*]thiophene. In the latter case it appears that the 2-bromine atom is hindering the oxidation either sterically or electronically.¹⁰⁷ Similar effects have been observed in the thiophene series.⁷¹⁶ In the presence of an excess of trifluoroperacetic acid Baeyer-Villiger oxidation of the acetyl group in each compound occurs.¹⁰⁷ It is noteworthy that Schlesinger and Mowry⁴⁷³ failed to oxidize a tetrachloro- and a pentachlorobenzo[*b*]thiophene with peracid. Each compound was known to contain chlorine atoms in the



2- and 3-positions and it was suggested that oxidation may be sterically hindered by the presence of a 7-chlorine substituent. Peracetic acid oxidation of **334** results in elimination of thiophenol to give **335** (RR' = methylenedioxy) and the corresponding 1,1-dioxide.⁵⁸² The sulfone may be prepared also by oxidation of the parent compound, and the sulfone of **335** ($R = \text{OMe}$, $R' = \text{H}$) may be prepared similarly.

The kinetics of oxidation of benzo[*b*]thiophene with perbenzoic acid⁷¹⁴ and peracetic acid⁷¹³ have been studied. The oxidation is more difficult than that of aliphatic or aromatic sulfides: the second stage occurs at about the same rate as the first.

⁷¹⁶ J. L. Melles and H. J. Backer, *Rec. Trav. Chim.* **72**, 314 (1953).

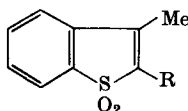
6-Nitro-, 5-hydroxy-, and 6-bromo-2,3-dihydro-benzo[*b*]thiophene-1,1-dioxide may be prepared from the corresponding amines by standard procedures; deamination of 5-amino-6-bromobenzo[*b*]thiophene-1,1-dioxide affords 6-bromobenzo[*b*]thiophene-1,1-dioxide.⁴²²

b. *Reactions of Benzo[*b*]thiophene-1,1-dioxides with Electrophiles.* Oxidation of the sulfur atom of benzo[*b*]thiophene and its derivatives invariably directs electrophilic substitution to the 6-position, irrespective of the substituent already present; nitration of benzo[*b*]thiophene-1,1-dioxide^{84, 538, 543} and its 2,3-dimethyl,¹⁰⁰ 5-acetamido,⁴²² and 2,3-dihydro⁵⁴³ derivatives and bromination of its 5-amino derivative⁴²² give the 6-substituted compound in each case. The unidentified mononitration product of 3-phenylbenzo[*b*]thiophene-1,1-dioxide is probably the 6-nitro derivative.²⁶⁶ Thioindoxyl-1,1-dioxide and its derivatives behave differently (Section, VI, P, 2, *g*).

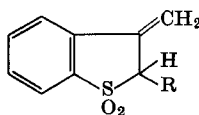
With chlorine, benzo[*b*]thiophene-1,1-dioxide affords 2,3-dichloro-2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide.⁴⁷³

c. *Reactions of Benzo[*b*]thiophene-1,1-dioxides with Nucleophiles.* 3-Halobenzo[*b*]thiophene-1,1-dioxides readily undergo normal nucleophilic displacement of the halogen atom.^{381, 473, 475, 484} In contrast, 2-bromobenzo[*b*]thiophene-1,1-dioxide is reported to give 3-ethoxybenzo[*b*]thiophene-1,1-dioxide on treatment with ethanolic sodium hydroxide.^{406a, 473, 717a}

The kinetics of the reactions of 2-chloromethylbenzo[*b*]thiophene-1,1-dioxide with piperidine, thiourea, and sodium thiophenoxide and of its 3-isomer with these reagents and with morpholine have been



(336)



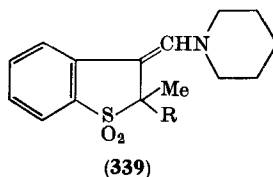
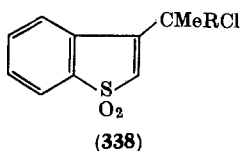
(337)

studied.⁷¹⁷ With each reagent, the 2-chloromethyl compound undergoes normal nucleophilic displacement of the halogen atom (S_N2 reaction), whereas the 3-chloromethyl compound, in every case, gives a 2-substituted 3-methylbenzo[*b*]thiophene-1,1-dioxide (336; R = piperidino, morpholino, $\dot{S}(:NH)NH_2$, or SPh) by an S_N2' nucleophilic

⁷¹⁷ F. G. Bordwell, F. Ross, and J. Weinstock, *J. Am. Chem. Soc.* **82**, 2878 (1960).

^{717a} T. Kauffmann, A. Risberg, J. Schulz, and R. Weber, *Tetrahedron Letters* 3563 (1964).

displacement reaction, followed by tautomerism of the intermediate (337). The structures of 2-piperidino- and of 2-morpholino-3-methylbenzo[b]thiophene-1,1-dioxide were established by their unambiguous synthesis from 2-bromo-3-methylbenzo[b]thiophene-1,1-dioxide by nucleophilic displacement of the halogen atom with piperidine or morpholine, respectively, and from their UV spectra. The piperidino compound gives the highly reactive 3-(methyl)thiooxindole-1,1-dioxide on acidic hydrolysis.⁷¹⁷ 2- and 3-bromomethyl- and 2- and 3-iodomethylbenzo[b]thiophene-1,1-dioxide behave analogously.⁴⁹⁶



When the 3-(1-chloroalkyl)benzo[b]thiophene-1,1-dioxides (338; R = H or Me) are treated with piperidine, they readily form the enamines (339; R = H or Me).^{717b} The mechanism of these reactions involves an S_N2' nucleophilic displacement followed by a rearrangement.

The 2,3-double bond in benzo[b]thiophene-1,1-dioxides undergoes addition reactions with nucleophiles in a manner comparable to that of other α,β -unsaturated sulfones; no aromatic properties are detectable in this way for the thiophene ring.⁷¹⁸⁻⁷²³ For example, thiophenol and *p*-thiocresol give the adducts (340; R = H or Me) in the presence of base.⁷²³ However, if the aryl mercaptan and the sulfone are heated together, a radical reaction occurs to give the corresponding 2-substituted compound.⁷²³ In contrast to the behavior of aryl mercap-

^{717b} F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Am. Chem. Soc.* **89**, 7144 (1967).

⁷¹⁸ F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.* **72**, 1985 (1950).

⁷¹⁹ W. H. McKellin and F. G. Bordwell, U.S. Patent 2,557,673 (1951); *Chem. Abstr.* **46**, 143 (1952).

⁷²⁰ W. H. McKellin and F. G. Bordwell, U.S. Patent 2,610,183 (1952); *Chem. Abstr.* **47**, 4913 (1953).

⁷²¹ W. H. McKellin, F. G. Bordwell, and O. C. Elmer, U.S. Patent 2,648,677 (1953); *Chem. Abstr.* **48**, 8264 (1954).

⁷²² J. W. Cusic, U.S. Patent 2,666,762 (1954); *Chem. Abstr.* **49**, 379 (1955); U.S. Patent 2,666,763 (1954); *Chem. Abstr.* **49**, 380 (1955).

⁷²³ F. G. Bordwell, R. D. Chapman, and W. H. McKellin, *J. Am. Chem. Soc.* **76**, 3637 (1954).

dioxides behave both as dienes and dienophiles in Diels–Alder reactions. Benzo[*b*]thiophene-1,1-dioxide affords adducts with butadiene,⁷²⁴ dimethyl acetylenedicarboxylate,⁷²⁵ cyclopentadiene,⁷²⁶ hexachlorocyclopentadiene,⁷²⁴ anthracene,⁷²⁶ tetracene,⁷²⁶ and 1-vinylnaphthalene.⁷²⁶ The dimethyl acetylenedicarboxylate adduct (**341**) loses sulfur dioxide to give dimethyl naphthalene-1,2-dicarboxylate,⁷²⁵ and the 1-vinylnaphthalene adduct (**342**) isomerizes to give **343**.⁷²⁶ Benzo[*b*]thiophene-3-carboxylic acid 1,1-dioxide⁷²⁷ and 3,5,6-trichlorobenzo[*b*]thiophene-1,1-dioxide⁷²⁸ similarly afford adducts with butadiene and cyclopentadiene, respectively. In contrast, benzo[*b*]thiophene-1,1-dioxide is reported not to form adducts with diethyl acetylenedicarboxylate,⁷²⁶ maleic anhydride,^{725, 726} 2-vinylnaphthalene,⁷²⁶ dicyclohex-1-enyl,⁷²⁶ or *p*-benzoquinone.⁷²⁶ 3,4-Dimethylthiophene-1,1-dioxide and benzo[*b*]thiophene-1,1-dioxide afford a bisadduct (either **344** or **345**) with loss of sulfur dioxide.⁷²⁶

In contrast to the adducts of many dienes with maleic anhydride, the above adducts are characteristically stable to heat; some do not dissociate at temperatures as high as 300°. This property is apparently associated with the sulfone group, since reduction of the anthracene adduct (**346**) with lithium aluminum hydride affords the corresponding cyclic sulfide, which readily dissociates at 250° to give anthracene and benzo[*b*]thiophene.⁷²⁶

On being heated in an inert solvent (e.g., tetralin) at 180°–200°, benzo[*b*]thiophene-1,1-dioxide affords 6*a*,11*a*-dihydrobenzo[*b*]naphtho[1,2-*d*]thiophene-7,7-dioxide (**347a**) through formation of the intermediate adduct **349**, which readily loses sulfur dioxide.^{377, 479, 729, 730} The kinetics of this self-condensation in various solvents have been studied recently.⁷³⁰ The product (**347a**) may be aromatized with palladium–charcoal,^{377, 479} or by treating its dibromide with base,⁷²⁹ to give the sulfone (**348a**) of benzo[*b*]naphtho[1,2-*d*]thiophene, which

⁷²⁴ O. C. Elmer, U.S. Patent 2,664,426 (1953); *Chem. Abstr.* **49**, 1106 (1955).

⁷²⁵ E. W. Duck, *Research Correspondence Suppl. to Research (London)* **8**, S-47 (1955); *Chem. Abstr.* **50**, 9376 (1956).

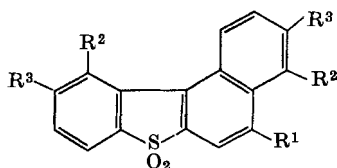
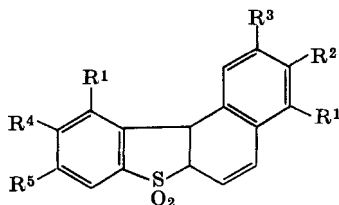
⁷²⁶ W. Davies and Q. N. Porter, *J. Chem. Soc.* 459 (1957).

⁷²⁷ E. F. Godefroi, U.S. Patent 3,111,527 (1963); *Chem. Abstr.* **60**, 2895 (1964).

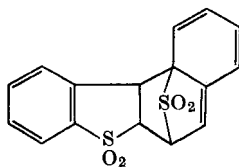
⁷²⁸ R. M. Bimber, H. Bluestone, and I. Rosen, U.S. Patent 3,130,199 (1964); *Chem. Abstr.* **61**, 3073 (1964).

⁷²⁹ F. G. Bordwell, W. H. McKellin, and D. Babcock, *J. Am. Chem. Soc.* **73**, 5566 (1951).

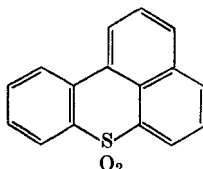
⁷³⁰ W. F. Taylor and T. J. Wallace, *Tetrahedron* **24**, 5081 (1968).

(347a) $R^1 = R^2 = R^3 = R^4 = R^5 = H$ (348a) $R^1 = R^2 = R^3 = H$ (347b) $R^2 = R^4 = Br; R^1 = R^3 = R^5 = H$ (348b) $R^1 = Br; R^2 = R^3 = H$ (347c) $R^1 = NO_2; R^2 = R^3 = R^4 = R^5 = H$ (348c) $R^1 = Cl; R^2 = R^3 = H$ (347d) $R^2 = R^4 = NO_2; R^1 = R^3 = R^5 = H$ (348d) $R^2 = NO_2; R^1 = R^3 = H$ (347e) $R^5 = NO_2; R^1 = R^2 = R^3 = R^4 = H$ (348e) $R^3 = NO_2; R^1 = R^2 = H$ (347f) $R^3 = NO_2; R^1 = R^2 = R^4 = R^5 = H$

is also formed in small amounts when benzo[*b*]thiophene is oxidized at 110° by peracetic acid to its 1,1-dioxide.^{377, 479} When benzo[*b*]thiophene-1,1-dioxide is distilled, a small amount of benzo[*b*]naphtho[1,2-*d*]thiophene is obtained.^{377, 479} If benzo[*b*]thiophene-1,1-dioxide is heated at 195° in the absence of a solvent, the products are the sulfone (347a) and benzo[*k*,1]thioxanthene-7,7-dioxide (350).^{470, 475}



(349)



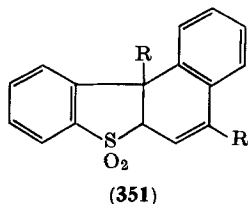
(350)

Taylor *et al.*⁷³¹ have recently studied the fragmentation of sulfone 347a in a mass spectrometer; the major fragmentation is by loss of SO₂ to give 1-phenylnaphthalene. Loss of H₂, H₂O, and H₂O₂ (or of O₂ followed by H₂) also occurs to give benzo[*b*]naphtho[1,2-*d*]thiophene and the corresponding sulfone (348a) and sulfoxide.

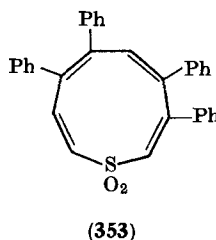
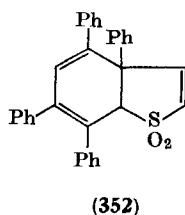
The sulfones of 3-methyl-, 3-methoxy-, 3-dimethylamino-, and 3-piperidinobenzo[*b*]thiophene yield only sulfur dioxide and intractable tars on being heated in inert solvents, whereas 2-bromo- and 2,3-dichlorobenzo[*b*]thiophene-1,1-dioxide are extremely stable to

⁷³¹ W. F. Taylor, J. M. Kelliher, and T. J. Wallace, *Chem. & Ind. (London)* 651 (1968).

heat.⁴⁷⁵ However, 5-bromobenzo[*b*]thiophene-1,1-dioxide affords **347b** and 3-bromo- and 3-chlorobenzo[*b*]thiophene-1,1-dioxide "dimerize" at unusually high temperatures (the chloro compound at



280°) to give, initially, **351** (R = Br or Cl).⁴⁷⁵ The bromo adduct readily loses hydrogen bromide to give **348b**, and the chloro adduct with base gives **348c**. 4-Nitrobenzo[*b*]thiophene-1,1-dioxide undergoes self-condensation to give **347c**, and peracid oxidation of 4-nitrobenzo[*b*]thiophene affords the corresponding sulfone, together with a small amount of **348d**.⁵³⁸ Likewise, 5-nitrobenzo[*b*]thiophene affords **348e** on peracid oxidation, and its sulfone undergoes self-condensation to give **347d**.⁵³⁸ 6-Nitrobenzo[*b*]thiophene-1,1-dioxide affords only sulfur dioxide and intractable tars when heated alone in an inert solvent.⁵³⁸ In the presence of benzo[*b*]thiophene-1,1-dioxide, however, **347a**, **347e**, and **347f** are obtained.⁵³⁸



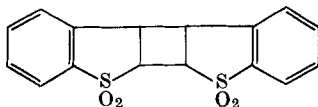
On being heated at 280°–300° sulfone (**108**) affords sulfur dioxide, phenylacetylene, 1,2,4-triphenylbenzene, and a small amount of 1,2,4,5-tetraphenylbenzene.³⁷⁴ Sulfone **108** is assumed to undergo valence tautomerism to give **352** through formation of **353**.

Irradiation of a benzene solution of benzo[*b*]thiophene-1,1-dioxide in bright sunlight for long periods affords a crystalline dimer for which structure **354** has been proposed.^{585, 732, 733} On being heated, the

⁷³² W. Davies and F. C. James, *J. Chem. Soc.* 314 (1955).

⁷³³ A. Mustafa, *Nature* **175**, 992 (1955).

dimer affords **347a**.⁷³² 3-Bromo-,⁷³² 2-bromo-, 7-chloro, 2-, 3-, 5-, 6-, and 7-methylbenzo[*b*]thiophene-1,1-dioxide afford similar dimers, whereas 2,3-dimethyl-, 3-methoxy-, and 3-acetoxy-5-methylbenzo[*b*]thiophene-1,1-dioxide are stable under identical conditions.^{585, 733}



(354)

In the presence of sodium hydroxide at 300° benzo[*b*]thiophene-1,1-dioxide decomposes to give a mixture of sodium *o*-methylbenzenesulfonate, sodium *o*-methylphenoxide, sodium sulfite, and sodium carbonate as the major products, together with smaller amounts of benzene and other (unidentified) products.⁷³⁴

e. *Miscellaneous Reactions and Uses of Benzo[*b*]thiophene-1,1-dioxides*. Benzo[*b*]thiophene-1,1-dioxide is deuterated in the 2-position with deuterium oxide in deuteropyridine at 100°. ¹²⁷ The ammonium N-*d*₄ salt of (+)-**18** affords 2-*d*-2-methyl-2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide on decarboxylation in a mixture of deuterium oxide and deuterioacetic acid.²¹⁵

The sulfones of 4-benzo[*b*]thienyl-*N*-methylcarbamate and its 2,3-dihydro derivative possess insecticidal activity.⁶¹⁰ Several merocyanine dyes have been prepared from thioindoxyl-1,1-dioxide,^{735, 736} and a number of 2-arylbenzo[*b*]thiophene-1,1-dioxides are fluorescent and are useful commercially (e.g., as dyes⁷³⁷ and in photographic films⁷³⁸). 2-(*p*-Isocyanatophenyl)benzo[*b*]thiophene-1,1-dioxide has been incorporated in copolymers of use in the printing industry.³⁰²

⁷³⁴ T. J. Wallace and B. N. Heimlich, *Tetrahedron* **24**, 1311 (1968).

⁷³⁵ L. G. S. Brooker and D. W. Heseltine, British Patent 776,414 (1957); *Chem. Abstr.* **51**, 12714 (1957); U.S. Patent 2,748,114 (1956); *Chem. Abstr.* **51**, 906 (1957).

⁷³⁶ L. G. S. Brooker and F. L. White, U.S. Patent 2,882,159 (1959); *Chem. Abstr.* **53**, 12900 (1959).

⁷³⁷ O. Dann, British Patent 871,351 (1961); *Chem. Abstr.* **56**, 3455 (1962); German Patent 1,063,571 (1959); *Chem. Abstr.* **55**, 12867 (1961).

⁷³⁸ R. Blank, H. Gold, K. L. Huppert, R. Matejec, R. Raue, and O. Dann, German Patent 1,147,328 (1963); *Chem. Abstr.* **59**, 4719 (1963).

f. *Hydrobenzo[b]thiophene-1,1-dioxides*. 2,3-Dihydrobenzo[b]thiophene-1,1-dioxides may be prepared by oxidation of the parent dihydro compound (see, e.g., Carruthers *et al.*⁴²⁶ and Ford and Young⁷¹³) or by reduction of the corresponding benzo[b]thiophene-1,1-dioxide with zinc and sodium hydroxide²⁶⁷ (note that zinc, acetic acid, and hydrochloric acid give the parent benzo[b]thiophene⁷³⁹) or catalytically.^{215, 264, 268, 281, 318, 422, 475, 543, 610, 718, 739-745} If the starting material contains a halogen atom, this may be removed,³⁸¹ and if it is a nitro compound, the product is invariably an amine.^{422, 475, 543} Catalytic reduction of the sulfone (49a) (Section IV, A) or, preferably, its dibromide, affords *cis*-octahydrobenzo[b]thiophene-1,1-dioxide, which may be prepared also by similar reduction of *cis*-2,3,3a,4,7,7a-hexahydrobenzo[b]thiophene-1,1-dioxide (Section IV, H, 1).²⁷ *cis*-Octahydrobenzo[b]thiophene-1,1-dioxide isomerizes to its *trans* isomer on treatment with ethanolic alkali.²⁷

Benzo[b]thiophene is inert to lithium aluminum hydride, but its 1,1-dioxide^{32, 739, 746} and 2,3-dihydrobenzo[b]thiophene-1,1-dioxide⁷³⁹ are both reduced to 2,3-dihydrobenzo[b]thiophene. It appears that the rather slow reduction of benzo[b]thiophene-1,1-dioxide first gives 2,3-dihydrobenzo[b]thiophene-1,1-dioxide, which is then rapidly reduced further.^{739, 746} 3-Aryl- and 3-alkyl-2,3-dihydrobenzo[b]thiophene-1,1-dioxides are readily reduced by lithium aluminum hydride to the corresponding 3-substituted 2,3-dihydrobenzo[b]thiophene.⁷⁴⁰⁻⁷⁴⁴ Similar reduction of a 2- or 3-alkyl- or a 2- or 3-alkoxybenzo[b]thiophene-1,1-dioxide, however, affords a mixture of the parent benzo[b]thiophene and its 2,3-dihydro derivative.^{32, 747} Steric or electronic

⁷³⁹ F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.* **73**, 2251 (1951).

⁷⁴⁰ E. N. Karaulova, D. Sh. Meilanova, and G. D. Gal'pern, *Dokl. Akad. Nauk SSSR* **123**, 99 (1958); *Chem. Abstr.* **53**, 5229 (1959).

⁷⁴¹ E. N. Karaulova, D. Sh. Meilanova, and G. D. Gal'pern, *Khim. Sera-i Azotorgan. Soedin., Soderzhashch. v Neft. i Nefteprod., Akad. Nauk SSSR, Bashkirsk. Filial* **3**, 25 (1960); *Chem. Abstr.* **59**, 1568 (1963).

⁷⁴² E. N. Karaulova, D. Sh. Meilanova, and G. D. Gal'pern, *Zh. Obshch. Khim.* **30**, 3292 (1960); *Chem. Abstr.* **55**, 19892 (1961).

⁷⁴³ I. U. Numanov, I. M. Nasyrov, G. D. Gal'pern, and A. A. Bakaev, *Dokl. Akad. Nauk Tadzh. SSR* **8**, 16 (1965); *Chem. Abstr.* **65**, 3805 (1966).

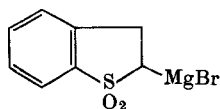
⁷⁴⁴ I. M. Nasyrov, I. U. Numanov, G. D. Gal'pern, and A. A. Bakaev, *Dokl. Akad. Nauk Tadzh. SSR* **9**, 23 (1966); *Chem. Abstr.* **65**, 18549 (1966).

⁷⁴⁵ I. U. Numanov, I. M. Nasyrov, and N. A. Yusupova, *Dokl. Akad. Nauk Tadzh. SSR* **10**, 29 (1967); *Chem. Abstr.* **68**, 104873 (1968).

⁷⁴⁶ G. Van Zyl and R. A. Koster, *J. Org. Chem.* **29**, 3558 (1964).

⁷⁴⁷ D. S. Rao, *Abstr. Papers, 137th Meeting Am. Chem. Soc., Cleveland* 26-O (1960).

effects may be responsible for this behavior.⁷⁴⁷ Lithium aluminum hydride alone will reduce 3-aminobenzo[*b*]thiophene-1,1-dioxides to the corresponding 3-aminobenzo[*b*]thiophene^{539, 541, 746}; in the presence of aluminum chloride partial reduction of the 2,3-double bond may also occur.^{539, 746, 748, 749} The sulfone group in benzo[*b*]thiophene-1,1-dioxide polarizes the 2,3-double bond making it susceptible to attack by the nucleophilic aluminohydride anion. Substituents influence the polarity of the bond, alkyl groups by hyperconjugation, and amino and alkoxy groups by a mesomeric effect. Resistance of the bond to nucleophilic attack in these cases is increased.



(355)

2,3-Dihydrobenzo[*b*]thiophene-1,1-dioxide is metallated by ethylmagnesium bromide in the 2-position to give the Grignard compound (355). Its 2-methyl,⁷⁴⁰⁻⁷⁴² 2-bromo,⁷¹⁸ or 2-ethoxycarbonyl²¹⁵ derivative may be prepared by treating 355 with methyl iodide, bromine, or ethyl chloroformate, respectively. 2-(Ethoxycarbonyl)thioindoxyl-1,1-dioxide may be methylated in the 2-position by successive treatment with sodium ethoxide and methyl iodide.²¹⁵

With chlorine or bromine, 3*a*,7*a*-dihydrobenzo[*b*]thiophene-1,1-dioxide (107) affords unidentified tetrahalogeno derivatives.⁷⁵⁰ Elimination of hydrogen chloride from 2,3-dichloro-2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide occurs on treatment with pyridine to give 2-chlorobenzo[*b*]thiophene-1,1-dioxide.⁴⁷³

Dehydrogenation of 6-amino-2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide with stannous chloride dihydrate is reported to afford 6-aminobenzo[*b*]thiophene-1,1-dioxide.⁴⁷⁵ It is noteworthy that 2-methyl-2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide undergoes ring opening with potassium *tert*-butoxide to give a quantitative yield of 2-propenylbenzenesulfinic acid.²⁷⁹

⁷⁴⁸ G. Van Zyl, C. J. Bredeweg, D. C. Neckers, R. H. Rynbrandt, E. D. Groenhof, and R. A. Koster, *6th Ann. Rept. Res., Petrol. Res. Fund, Am. Chem. Soc.* 13 (1961).

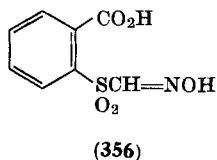
⁷⁴⁹ G. Van Zyl, R. H. Rynbrandt, C. J. Bredeweg, D. C. Neckers, and R. A. Koster, *8th Ann. Rept. Res., Petrol. Res. Fund, Am. Chem. Soc.* 4 (1963).

⁷⁵⁰ J. E. Mahan and A. C. Rothlisberger, U.S. Patent 2,682,545 (1954); *Chem. Abstr.* 49, 11019 (1955).

g. *Thioindoxyl-1,1-dioxides*. Thioindoxyl-1,1-dioxide (**60**) may be prepared by oxidation of the parent compound, by acidic hydrolysis of 3-diethylaminobenzo[*b*]thiophene-1,1-dioxide,⁴⁷⁵ or by decarboxylation of the corresponding 2-carboxylic acid.^{271, 751} Its hydrazone is obtained when 3-chloro-2-dimethylaminomethylbenzo[*b*]thiophene-1,1-dioxide is treated with an excess of hydrazine hydrate, and the same product is formed from the methiodide.³⁸¹ 2-(2-Naphthyl)-⁴⁸⁴ and 2-methyl-6-chlorothioindoxyl-1,1-dioxide³⁸¹ may be prepared by acidic hydrolysis of the corresponding 3-dialkylamino derivative. Other syntheses of thioindoxyl-1,1-dioxide and its derivatives are described in Section IV.

The spectroscopic properties (Section III, B) of thioindoxyl-1,1-dioxide and its 2-(2-naphthyl)⁴⁸⁴ and 2-methyl-6-chloro³⁸¹ derivative show that they exist predominantly in their keto forms. However, treatment of 2-(2-naphthyl)thioindoxyl-1,1-dioxide with diazo-methane affords only an *O*-methyl derivative.⁴⁸⁴

Thioindoxyl-1,1-dioxide undergoes ring fission with alkali⁷⁵² or with sodium nitrite in acetic acid⁷⁵³ to give *o*-methylsulfonylbenzoic



acid or **356**, respectively. On treatment with base, 2-(2-naphthyl)thioindoxyl-1,1-dioxide and its *O*-methyl derivative each affords *o*-(2-naphthylmethylsulfonyl)benzoic acid.⁴⁸⁴

Wolff-Kishner reduction of thioindoxyl-1,1-dioxide gives 2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide.^{543, 754}

Thioindoxyl-1,1-dioxide is monobrominated^{271, 751} and mononitrated^{751, 755} in the 2-position. The mononitro derivative reacts with bromine, chlorine, or iodine to give the corresponding 2-halo-2-nitro-

⁷⁵¹ M. Mackanova, *Tsiklicheskie β-Diketony*, *Akad. Nauk Latv. SSR, Inst. Organ. Sintēza* 285 (1961); *Chem. Abstr.* **55**, 27231 (1961).

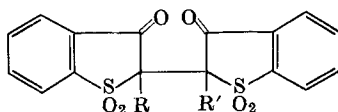
⁷⁵² R. G. Pearson, D. H. Anderson, and L. L. Alt, *J. Am. Chem. Soc.* **77**, 527 (1955).

⁷⁵³ A. Mustafa and M. M. Sallam, *J. Am. Chem. Soc.* **81**, 1980 (1959).

⁷⁵⁴ H. Kloosterziel and H. J. Backer, *Rec. Trav. Chim.* **71**, 361 (1952).

⁷⁵⁵ M. Mackanova and G. Vanags, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* 543 (1962); *Chem. Abstr.* **59**, 6341 (1963).

2,3-dihydrobenzo[*b*]thiophen-3-one-1,1-dioxide, and is hydrolyzed by water to give a compound which is assumed to be *o*-(nitromethylsulfonyl)benzoic acid.^{751, 755} With concentrated sulfuric acid it gives saccharin and hydroxylamine.^{751, 755} The monobromo derivative is brominated further in the 2-position to give 2,2-dibromo-2,3-dihydrobenzo[*b*]thiophen-3-one-1,1-dioxide.^{271, 751} 2-Bromo- and 2-chloro-2-nitro-2,3-dihydrobenzo[*b*]thiophen-3-one-1,1-dioxide afford *o*-sulfonylbenzoic acid on treatment with aqueous alkali; the bromo

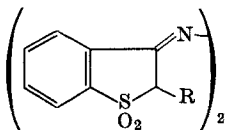


(357)

compound is said to give **357** ($R = \text{NO}_2$, $R' = \text{Br}$) on being heated in benzene.⁷⁵⁵ Treatment of 2-(2-naphthyl)thioindoxyl-1,1-dioxide with bromine or potassium ferricyanide affords **357** ($R = R' = 2\text{-naphthyl}$).⁴⁸⁴ 2-(Ethoxycarbonyl)thioindoxyl-1,1-dioxide is also brominated in the 2-position.^{271, 751}

With thiophenol in the presence of zinc chloride and hydrochloric acid, thioindoxyl-1,1-dioxide and related compounds give 3-phenylthiobenzo[*b*]thiophene-1,1-dioxides, which afford the corresponding 2,3-dihydrobenzo[*b*]thiophene-1,1-dioxide on reduction with zinc and sodium hydroxide.⁷⁵⁶

When thioindoxyl-1,1-dioxide is treated with phosphorus pentachloride, it gives 3-chlorobenzo[*b*]thiophene-1,1-dioxide.⁴⁷⁵



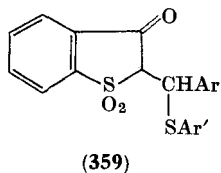
(358)

With hydrazine hydrochloride, thioindoxyl-1,1-dioxide affords the azine (**358**; $R = \text{H}$), which affords **358** [$R = \text{Br}$] with bromine and [$R = \text{NO}_2$] with nitric acid].^{271, 751}

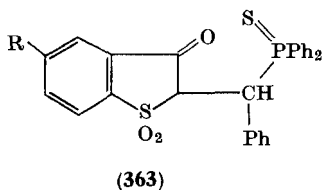
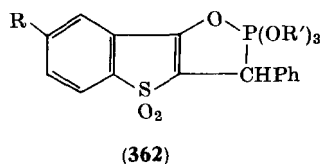
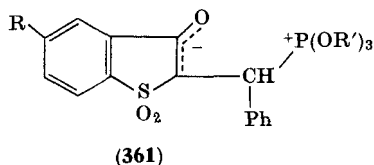
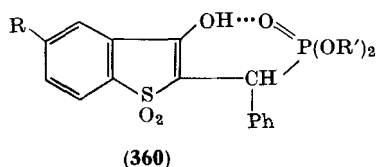
The methylene group of thioindoxyl-1,1-dioxide condenses with aromatic aldehydes^{271, 753, 756, 757} and cyclopentanone.⁴⁵¹ 2-Arylidene-2,3-dihydrobenzo[*b*]thiophen-3-one-1,1-dioxides give adducts

⁷⁵⁶ A. Mustafa and S. M. A. D. Zayed, *J. Am. Chem. Soc.* **79**, 3500 (1957).

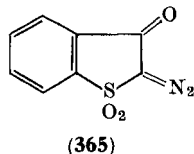
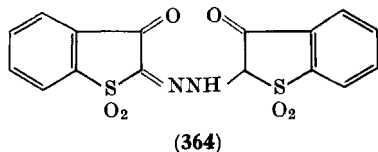
⁷⁵⁷ W. Asker, A. F. A. M. Shalaby, and S. M. A. D. Zayed, *J. Org. Chem.* **23**, 1781 (1958).



(359) with aryl thiols.^{753, 756, 757} 2-Benzylidene-2,3-dihydrobenzo[*b*]-thiophen-3-one-1,1-dioxide and its 5-methyl derivative react with



trialkyl phosphites in phenol to give compounds with the general formula (360; R = H or Me, R' = Me, Et, or Prⁱ); in benzene the 1:1 adducts isolated are believed to have either the dipolar structure (361; R = H or Me, R' = Me, Et, or Prⁱ), or the corresponding cyclic oxyphosphorane structure (362).⁷⁵⁸ Dialkyl phosphites react to give the 1:1 adducts (360) and diphenylphosphinodithioic acid reacts similarly to give 1:1 adducts (363; R = H or Me).⁷⁵⁸



The hydrazone (364) may be prepared by treating thioindoxyl-1,1-dioxide with *p*-tosylazide; on being heated the product is decomposed to give starting material and the α -diazo- β -ketosulfone (365). Various reactions of 364 and 365 have been described.³²⁷

⁷⁵⁸ A. Mustafa, M. M. Sidky, S. M. A. D. Zayed, and W. M. Abdo, *Tetrahedron* **24**, 4725 (1968).

VII. Metallation of Benzo[*b*]thiophenes

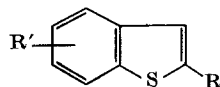
Benzo[*b*]thiophene has been metallated in the 2-position using ethylmagnesium bromide, sodamide, sodium metal, and mercuric acetate.⁷⁵⁹ In preparing benzo[*b*]thiophene-3-carboxylic acid from 3-bromobenzo[*b*]thiophene by its reaction with ethylmagnesium bromide, followed by carbonation of the resulting mixture, Badger *et al.*³¹⁵ obtained a significant quantity of benzo[*b*]thiophene-2,3-dicarboxylic acid, which was also prepared in 10% yield by treating benzo[*b*]thiophene-3-carboxylic acid with ethylmagnesium bromide, followed by carbonation. Capps and Hamilton⁵²⁹ have used 2-sodio-benzo[*b*]thiophene to prepare 2-hydroxyethylbenzo[*b*]thiophene by reaction with ethylene oxide, and Bordwell *et al.*⁴⁹⁶ have prepared 2-acetoxymercuri-3-methylbenzo[*b*]thiophene and treated it with iodine to give 2-iodo-3-methylbenzo[*b*]thiophene.

The metallation of benzo[*b*]thiophene with *n*-butyllithium was first reported by Shirley and Cameron⁷⁵⁹ in 1950. 2-Benzo[*b*]thienyllithium and its ring-substituted derivatives are obtained rapidly and almost quantitatively by this reaction and are useful intermediates for the preparation of a wide range of 2-substituted benzo[*b*]thiophenes (Table XVII). Only one benzo[*b*]thiophene having a lithium atom in a position other than the 2-position has been prepared by direct metallation; Matsuki and Adachi¹⁸³ prepared 2-methoxy-3-benzo[*b*]thienyllithium by direct metallation of 2-methoxybenzo[*b*]thiophene. It has the expected properties. In an attempt to prepare the ethyl ester of **306** by treating 2-benzo[*b*]thienyllithium with ethyl pyruvate, Sjöberg²⁰⁸ found that both carbonyl groups of the ester reacted. 2-Benzo[*b*]thienyllithium was therefore treated with magnesium bromide etherate to give the corresponding Grignard compound, which reacted normally with ethyl pyruvate to give the required ester. This procedure is used for the preparation of 2-benzo[*b*]thienyllithium because 2-halobenzo[*b*]thiophenes are not available directly from benzo[*b*]thiophene (Section VI, D); they are prepared by treating 2-benzo[*b*]thienyllithium with the appropriate halogen (FCIO₃ in the case of fluorine) (Table XVII).

Shirley and Goan⁷⁶⁰ have shown that the competitive metallation of benzo[*b*]thiophene and *N*-methylindole affords only 2-benzo[*b*]-

⁷⁵⁹ See e.g., D. A. Shirley and M. D. Cameron, *J. Am. Chem. Soc.* **72**, 2788 (1950).

⁷⁶⁰ D. A. Shirley and J. C. Goan, *J. Organometal. Chem. (Amsterdam)* **2**, 304 (1964).

2-SUBSTITUTED BENZO[*b*]THIOPHENES SYNTHESIZED FROM 2-BENZO[*b*]THIENYL LITHIUMS


R	R'	Reagent	Yield (%)	Ref.
Me	H	<i>p</i> -MeC ₆ H ₄ SO ₂ Me	43, 51	564, 759, 506
		Me ₂ SO ₄	91	740, 741, 742
Et	H	<i>p</i> -MeC ₆ H ₄ SO ₂ Et	20-30	132
		Et ₂ SO ₄	70-80, 81	132, 740, 741, 742
		EtI	20	132
		EtBr	10	132
Ph	H	C ₆ H ₅ F	55	185, 307
		C ₆ H ₅ Cl/piperidine	64	483
2-Benzo[<i>b</i>]thienyl	H	CuCl ₂	36	305
2-Benzo[<i>b</i>]thienyl	H	Br ₂	16	564, 759
Br	H		39	
CH ₂ Ph	H	C ₆ H ₅ CH ₂ Cl	41.5	132
CH ₂ C ₆ H ₄ OMe- <i>p</i>	H	<i>p</i> -MeOC ₆ H ₄ CH ₂ Cl	?	464
F	H	FCIO ₃	70	482
Cl	H	Cl ₂	48, ?	412, 749
		C ₆ H ₅ SO ₂ Cl	?	760a
Br	H	Br ₂	65, 84	406, 183
I	H	I ₂	29	413
CHO	H	C ₆ H ₅ NMeCHO	62, 77	640, 520
CO ₂ H	H	CO ₂	55, 62, 82	564, 759, 687, 685
COMe	H	CH ₃ CO ₂ Li	54	654, 464
COPh	H	C ₆ H ₅ CO ₂ Li	49	132
CO(2-benzo[<i>b</i>]thienyl)	H	<i>N,N</i> -Dimethylcarbonyl chloride	?	667
COC ₆ H ₄ CH ₂ Ph- <i>o</i>	H	<i>o</i> -PhCH ₂ C ₆ H ₄ CN ^a	66	504

continued

TABLE XVII—continued

R	R'	Reagent	Yield (%)	Ref.
COC ₆ H ₄ CH ₂ (1-naphthyl)- <i>o</i>	H	<i>o</i> -(1-naphthyl)CH ₂ C ₆ H ₄ CN ^a	44	504
COC ₆ H ₄ CH ₂ (2-naphthyl)- <i>o</i>	H	<i>o</i> -(2-naphthyl)CH ₂ C ₆ H ₄ CN ^a	65	504
CONHPh	H	C ₆ H ₅ NCO	81	564, 759
CONHC ₆ H ₄ Me- <i>o</i>	H	<i>o</i> -MeC ₆ H ₄ NCO	41	564, 759
OH	H	O ₂	40	539, 541
CH ₂ OH	H	HCHO	89	528
CH(OH)Me	H	CH ₃ CHO	72	564, 759
CH(OH)Ph	H	C ₆ H ₅ CHO	70	564, 759
CH(OH)C ₆ H ₄ Me- <i>p</i>	H	<i>p</i> -MeC ₆ H ₄ CHO	low	564, 759
CH(OH)C ₆ H ₄ Cl- <i>p</i>	H	<i>p</i> -ClC ₆ H ₄ CHO	68	564, 759
CH(OH)C ₆ H ₄ NMe ₂ - <i>p</i>	H	<i>p</i> -Me ₂ NC ₆ H ₄ CHO	47	564, 759
CMe(OH)Ph	H	C ₆ H ₅ COMe	77	467
1-Hydroxycyclohexyl	H	Cyclohexanone	82	483
SH	H	S	58	506, 507, 700
		MeCHCH ₂	?	701
		$\begin{array}{c} \diagup \\ \text{S} \end{array}$		
SEt	H	S, followed by EtI	69	639
SPh	H	(C ₆ H ₅ S) ₂	?	700, 760b
SCH ₂ CH(OMe) ₂	H	[(MeO) ₂ CHCH ₂ S] ₂	69	290
SiMe ₃	H	Me ₃ SiCl	25	391, 392
SiPh ₃	H	Ph ₃ SiCl	71	390
B(OH) ₂	H	B(OMe) ₃	?	394
CH ₂ CH ₂ Cl	H	TsOCH ₂ CH ₂ Cl	48	509
CH ₂ =C(C ₈ H ₅ S) ^b	H	CH ₃ COCl	96.5	132
Benzo[<i>b</i>]thien-3-ylcarbinyI	H	C ₈ H ₅ S·CHO ^c	?	486
2-Hydroxy-1,3,3-trimethylindolin-2-yl	H	C ₁₁ H ₁₃ NO ^d	55	284

SH	3-Me	S	40	506
CHO	3-Me	C ₆ H ₅ NMeCHO	51	621
CO ₂ H	3-Me	CO ₂	65, 73	481, 521
CO ₂ H	4-Me	CO ₂	75	98
CO ₂ H	5-Me	CO ₂	73	98
CO ₂ H	6-Me	CO ₂	79	98
CHO	7-Me	HCONMe ₂	79	90
CO ₂ H	7-Me	CO ₂	89	90, 98
CH ₂ OH	7-Me	HCHO	64	90
CH(OH)Me	7-Me	CH ₃ CHO	?	90
7-Me-2-benzo[<i>b</i>]thienyl	7-Me	CuCl ₂	41	90
CH ₂ C ₆ H ₄ OMe- <i>p</i>	3-Et	<i>p</i> -MeOC ₆ H ₄ CH ₂ Cl	23.5	464
SH	3,5-Me ₂	S	43	506
SH	3,7-Me ₂	S	33	506
CHO	3-Br	C ₆ H ₅ NMeCHO	10	477, 621
CO ₂ H	3-Br	CO ₂	79	477
CHO	4-Br	HCONMe ₂	31	105
Br	5-Br	Br ₂	62	76
CHO	5-Br	HCONMe ₂	73	76
CO ₂ H	5-Br	CO ₂	68	76
5-Br-2-benzo[<i>b</i>]thienyl	5-Br	CuCl ₂	14	76
CHO	6-Br	HCONMe ₂	28	105
CHO	7-Br	HCONMe ₂	19	105
CHO	3-Cl	C ₆ H ₅ NMeCHO	?	621
CO ₂ H	3-OMe	CO ₂	94	183
CO ₂ H	6-OMe	CO ₂	33.5	42
3-OMe-2-benzo[<i>b</i>]thienyl	3-OMe	CuCl ₂	88	183

^a Followed by hydrolysis of intermediate ketimine with acid.

^b 1,1-Di(2-benzo[*b*]thienyl)ethylene.

^c Benzo[*b*]thiophene-3-carboxaldehyde.

^d 1,3,3-Trimethylindolin-2-one.

thienyllithium. *N*-Methyl-2-indolylithium metallates benzo[*b*]thiophene, but 2-benzo[*b*]thienyllithium does not metallate *N*-methylindole. Thus, in spite of the probable greater inductive effect of nitrogen, the metallation product is more stable at a position adjacent to a sulfur atom than to an *N*-methyl group.

Metallation of 4,4'-, 5,5'-, 6,6'-, and 7,7'-dibenzo[*b*]thienyl with two molar equivalents of *n*-butyllithium affords the corresponding 2,2'-dilithio compounds, which give the corresponding 2,2'-dicarboxylic acids on carbonation.⁵¹⁷

Metallation of 5-bromobenzo[*b*]thiophene with one molar equivalent of *n*-butyllithium affords 5-bromo-2-benzo[*b*]thienyllithium but, with 2 molar equivalents of *n*-butyllithium, metal-halogen exchange also occurs and a dilithium compound is obtained, which affords benzo[*b*]thiophene-2,5-dicarboxylic acid on carbonation.⁷⁶ 3-Bromo-2-fluorobenzo[*b*]thiophene similarly affords 2-fluoro-3-benzo[*b*]thienyllithium,⁴⁸² and 2,3-dibromobenzo[*b*]thiophene undergoes metal-halogen exchange with an excess of *n*-butyllithium to give only 3-bromo-2-benzo[*b*]thienyllithium.⁴⁷⁷ In the latter case the second bromine atom can be made to undergo metal-halogen exchange if the monolithio compound is treated with powdered lithium.⁵¹¹ 2,3-Dibenzo[*b*]thienyllithium may also be prepared by treating 3-bromobenzo[*b*]thiophene with two molar equivalents of *n*-butyllithium; it affords benzo[*b*]thiophene-2,3-dicarboxylic acid on carbonation.⁵¹¹ On hydrolysis with acid, 3-bromo-2-benzo[*b*]thienyllithium affords pure 3-bromobenzo[*b*]thiophene²⁹⁷; elemental bromination of benzo[*b*]thiophene under most conditions affords a mixture of the 2- and 3-bromo isomers (Section VI,D). Recently, Dickinson and Iddon²⁹⁷ have prepared 3-benzo[*b*]thienyllithium by treating 3-bromobenzo[*b*]thiophene with *n*-butyllithium in ether at -70° . Like 3-thienyllithium (and related compounds)^{761, 762} and 3-benzofuranyllithium,⁷⁶³ this lithium compound has a tendency to undergo lithium transfer reactions, and it must therefore be prepared and handled at low temperatures. It reacts with most of the reagents

^{760a} F. M. Gordon, U.S. Patent 3,218,229 (1965); *Chem. Abstr.* **64**, 7305 (1966).

^{760b} *Ann. Rept., Am. Petrol. Inst., Res. Project* **48**, No. 8, 64 (1954-1955).

⁷⁶¹ P. Moses and S. Gronowitz, *Arkiv Kemi* **18**, 119 (1962).

⁷⁶² S. Gronowitz, *Advan. Heterocyclic Chem.* **1**, 75 (1963), and references cited therein.

⁷⁶³ H. Gilman and D. S. Melstrom, *J. Am. Chem. Soc.* **70**, 1655 (1948).

with which 2-benzo[*b*]thienyllithium reacts, and has been shown to be a useful intermediate for the preparation of 3-substituted benzo[*b*]thiophenes. Some of these are normally prepared by using 3-benzo[*b*]thienylmagnesium halides, but this procedure suffers from the disadvantage that the Grignard compounds have to be synthesized using the entrainment procedure; yields are often variable. Ghaisas *et al.*⁶²¹ have treated 3-bromobenzo[*b*]thiophene with *n*-butyllithium in ether at room temperature. After treating the resulting reaction mixture with *N*-methylformanilide, a low yield (10%) of 3-bromobenzo[*b*]thiophene-2-carboxaldehyde was isolated. This low yield can now be explained by assuming that metal-halogen exchange also occurred under these conditions, leading to the formation of undetected benzo[*b*]thiophene-3-carboxaldehyde. 3-Chlorobenzo[*b*]thiophene-2-carboxaldehyde was prepared similarly from 3-chlorobenzo[*b*]thiophene, but no yield was given.⁶²¹ Metal-halogen exchange does not occur with 3-chlorobenzo[*b*]thiophene.

VIII. Hydrodesulfurization of Benzo[*b*]thiophenes

The use of hydrodesulfurization in the determination of the structures of unknown benzo[*b*]thiophenes is becoming increasingly recognized; about 100 examples have now been recorded. Two sets of experimental conditions are commonly used: the benzo[*b*]thiophene may be treated with Raney nickel alloy directly in alkaline medium (the method of Papa *et al.*⁷⁶⁴), or it may be boiled in ethanol with Raney nickel of varying reactivity (commonly W-7). Even under mild conditions, nonaromatic double bonds are usually saturated, halogens are removed, and nitro groups are reduced. Raney cobalt has about one-tenth the activity of Raney nickel in the hydrodesulfurization of benzo[*b*]thiophenes.⁷⁶⁵

Benzo[*b*]thiophenes are converted into cyclohexane derivatives by treatment with hydrogen over a heated palladium catalyst.^{21, 22, 766} If the reaction tube is coupled directly to the injection port of a GLC

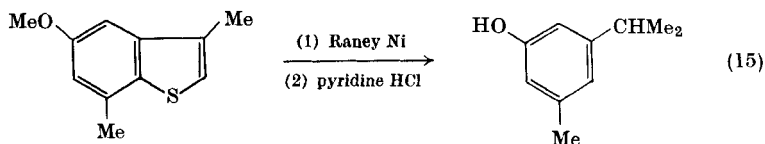
⁷⁶⁴ D. Papa, E. Schwenk, and H. F. Ginsberg, *J. Org. Chem.* **14**, 723 (1949).

⁷⁶⁵ G. M. Badger, N. Kowanko, and W. H. F. Sasse, *J. Chem. Soc.* 440 (1959).

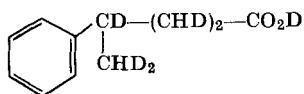
⁷⁶⁶ E. A. Walker, *4th Wilkins Gas Chromatog. Symp., Manchester*, 1966 15.

column, the structures of benzo[*b*]thiophenes may be established on a microscale.

Hydrodesulfurization of the mixture of isomers obtained by the nitration of benzo[*b*]thiophene gives a mixture of amines, the identification of which indicates the possible orientations of the nitro groups.^{84, 412} It should be noted, however, that 5- and 7-nitrobenzo[*b*]thiophene both give *m*-ethylaniline in this reaction.



Hydrodesulfurization of certain hydroxy-⁴³⁷ and methoxy-substituted⁶¹⁵ alkybenzo[*b*]thiophenes is a useful means of preparing some otherwise inaccessible alkyl-substituted phenols [e.g., Eq. (15)].⁶¹⁵ Various *p*-methoxyphenylbenzo[*b*]thiophenes have been employed similarly to prepare the corresponding hydroxydiphenylalkanes.⁴⁶⁴ Catalytic hydrodesulfurization of α -alkyl- β -(3-benzo[*b*]thienyl)propionic acids affords a convenient method of preparing α,γ -disubstituted γ -phenylbutyric acids.⁵³⁶ Treatment of β -(3-benzo[*b*]thienyl)acrylic acid with Raney nickel alloy, sodium methoxide, and deuterium oxide affords the deuterated acid (366).⁶⁹⁷

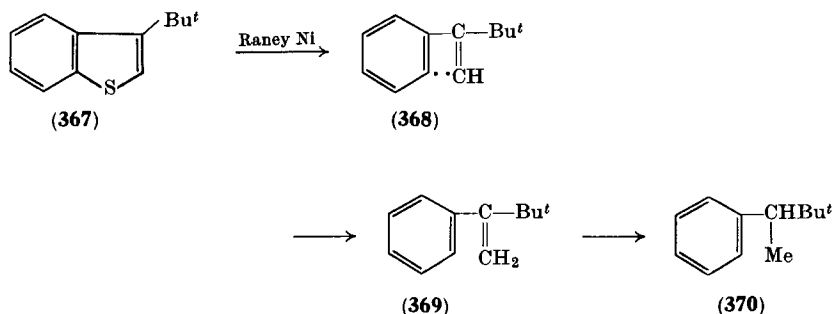


(366)

Hydrodesulfurization of 4-phenyl- or 4-(*o*-, *m*-, or *p*-tolyl)benzo[*b*]thiophene affords 2-ethyl- or 2-, 3-, or 4-methyl-2'-ethyldiphenyl, respectively.³⁵⁶ It is of interest that 4-aryl-6,7-dihydrobenzo[*b*]thiophenes afford 2-ethyl-4,5-dihydrodiphenyls.³⁵⁶

The mechanism of hydrodesulfurization of benzo[*b*]thiophene and its derivatives involves, as a first step, chemisorption of the molecules (through the sulfur atom lone pair of electrons) in a more or less perpendicular fashion to the catalyst surface. Removal of the sulfur is then thought to produce a diradical which, on subsequent hydro-

genation, affords the product.⁷⁶⁷⁻⁷⁶⁹ Corson *et al.*⁴¹⁶ obtained the olefin (**369**) (10% yield) together with **370** on hydrodesulfurization of 3-*tert*-butylbenzo[b]thiophene (**367**) (Scheme 7) with Raney nickel.



SCHEME 7

The olefin (**369**) is thought to arise by reaction of the intermediate diradical (**368**) with hydrogen before subsequent hydrogenation of **369** to **370**.⁷⁶⁷⁻⁷⁶⁹ When benzo[b]thiopheno[3,2-*b*]benzo[b]thiophene (**154**) is hydrodesulfurized, bibenzyl, *trans*-stilbene, and 2-phenylbenzo[b]thiophene are obtained in amounts determined by the catalyst and reaction conditions.⁷⁶⁸ This result lends support to the view that removal of sulfur precedes hydrogenation in hydrodesulfurization reactions.

The rates of hydrodesulfurization of benzo[b]thiophene^{770, 771} and its 3-methyl derivative⁷⁷² have been compared with those of other sulfur compounds using hydrogen and a $\text{CoO}_3\text{-MoO}_3\text{-Al}_2\text{O}_3$ catalyst.

The use of hydrodesulfurization to identify benzo[b]thiophenes in petroleum oils has been discussed in Section II, A.

⁷⁶⁷ G. M. Badger, G. Jackson, N. Kowanko, W. H. F. Sasse, and C. P. Whittle, *5th Ann. Rept. Res., Petrol. Res. Fund., Am. Chem. Soc.* **37** (1960).

⁷⁶⁸ G. M. Badger, N. Kowanko, and W. H. F. Sasse, *J. Chem. Soc.* **2969** (1960).

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⁷⁷⁰ R. D. Obolentsev and A. V. Mashkina, *Dokl. Akad. Nauk SSSR* **131**, 1092 (1960); *Chem. Abstr.* **54**, 19131 (1960).

⁷⁷¹ R. Papadopoulos and M. J. G. Wilson, *Chem. & Ind. (London)* **427** (1965).

⁷⁷² R. D. Obolentsev, A. V. Mashkina, A. R. Kuzyev, and G. P. Gribkova, *Khim. Seraorgan. Soedin., Soderzhashch. v Neft. i Nefteprod., Akad. Nauk SSSR, Bashkirsk. Filial* **4**, 166 (1961); *Chem. Abstr.* **57**, 15048 (1962).

APPENDIX

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Physicochemical Properties of Pyrroles

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I. Introduction

Earlier reviews of the chemistry of pyrrole and its derivatives have been concerned mainly with synthesis and reactions.¹⁻⁵ Discussion of the physicochemical properties has been avoided and only recently⁶ has any attempt to redress this neglect been made.

This review, which covers the literature up to mid-1968, presents the knowledge, which is available to date, concerning the molecular and electronic structure of pyrrole. It also surveys the spectroscopic and nonspectroscopic physical properties of pyrrole and its simple derivatives. During the past 25 years, as a result of developments and improvements in instrument design, the literature on the physicochemical properties of organic compounds has expanded rapidly. Mainly as a result of the instability or nonavailability of many compounds, however, the study of pyrroles has lagged somewhat behind

¹ H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. 1. Akad. Verlagsges., Leipzig, 1934.

² B. Oddo, in "Traité de chimie organique" (V. Grignard, ed.), Vol. 19, pp. 1-199. Masson, Paris, 1942.

³ A. H. Corwin, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 1, pp. 277-342. Wiley, New York, 1950.

⁴ A. Treibs, *Rev. Chim., Acad. Rep. Populaire Roumaine* **7**, 1345 (1962); *Chem. Abstr.* **61**, 4300 (1964).

⁵ E. Baltazzi and L. I. Krimen, *Chem. Rev.* **63**, 511 (1963).

⁶ K. Schofield, "Heteroaromatic Nitrogen Compounds: Pyrroles and Pyridines." Butterworth, London and Washington, D.C., 1967.

that of other heterocyclic systems. Deductions drawn from early data are sometimes suspect because of the doubtful purity of the compounds and the majority of more reliable results come from investigations of the more stable pyrroles having electron-withdrawing substituents. Recent improvements in synthetic and instrumental methods have enabled more accurate data to be accumulated. Considerable use has been made of infrared (IR) measurements, but interest has been moving recently to the newer techniques of nuclear magnetic resonance (NMR) and mass spectrometry, and isolated investigations using electron spin resonance (ESR)⁷⁻⁹ and magnetic susceptibility¹⁰⁻¹⁷ techniques have also been made on pyrrole-metal complexes and pyrrolyl radicals.

II. Structure of Pyrrole

A. MOLECULAR AND ELECTRONIC STRUCTURE AND AROMATICITY

Pyrrole (1) has a pentagonal structure of C_{2v} symmetry having all the atoms in a single plane. The orbital hybridization¹⁸ of the nitrogen atom approximates to sp^2 , although the possibility of a pyramidal hybridization, i.e., $sp^2 \sim sp^3$, was originally considered. Dipole moment studies allow the N-H bond an out-of-plane latitude of 7° (see Section III, A, 2) and the data from Raman and IR studies do not differentiate

⁷ V. A. Sharpatyi, *Proc. Radiation Chem. Symp., Tihany, Hungary*, 1962 p. 463 (1964); *Chem. Abstr.* **62**, 12631 (1965).

⁸ K. G. Yanova and V. A. Sharpatyi, *Opt. i Spektroskopiya Akad. Nauk SSSR, Otd. Fiz.-Mat. Nauk, Sb. Statei* **2**, 73 (1963); *Chem. Abstr.* **59**, 13518 (1963).

⁹ C. U. Deffner and E. Brunner, *Z. Physiol. Chem.* **343**, 218 (1966).

¹⁰ G. Bonino and R. Manzoni-Ansidei, *Chem. Ber.* **76**, 553 (1943).

¹¹ A. Pacault, *Ann. Chim. (Rome)* **1**, 527 (1946).

¹² V. I. Belova, Y. K. Syrkin, and A. I. Avdeeva, *Zh. Neorgan. Khim.* **2**, 1488 (1957); *Chem. Abstr.* **52**, 7797 (1958).

¹³ R. Havemann, W. Haberditzl, and P. Grzegorzewski, *Z. Physik. Chem. (Leipzig)* **217**, 91 (1961).

¹⁴ V. I. Belova and Y. K. Syrkin, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk* p. 1903 (1961); *Chem. Abstr.* **56**, 8154 (1962).

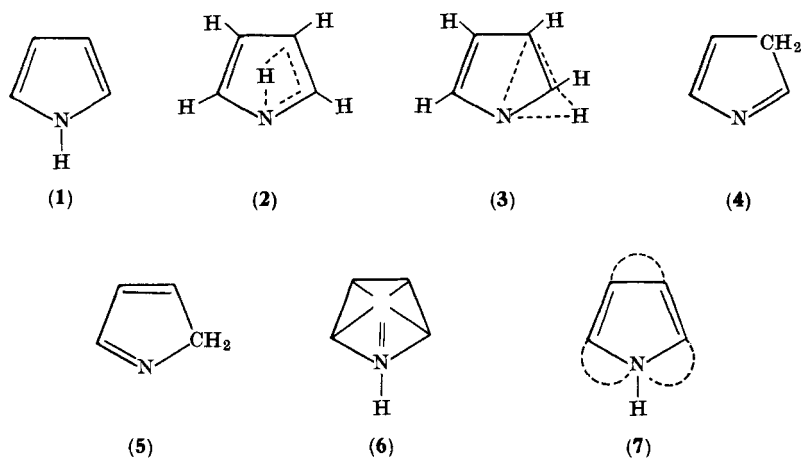
¹⁵ B. A. Kozlov and T. K. Rebane, *Zh. Fiz. Khim.* **36**, 143 (1961); *Chem. Abstr.* **59**, 40 (1963).

¹⁶ C. A. Bates, W. S. Moore, K. J. Standley, and K. W. H. Stevens, *Proc. Phys. Soc. (London)* **79**, 73 (1962).

¹⁷ D. Bertin, M. Gomel, and N. Lumbroso-Bader, *Compt. Rend.* **258**, 2301 (1964).

¹⁸ E. Clementi, H. Clementi, and D. R. Davis, *J. Chem. Phys.* **46**, 4725 (1967).

adequately between the planar C_{2v} and the nonplanar C_s symmetry systems (see Section III, B, 1, a). All nonplanar structures, however, were completely excluded by the microwave rotational spectrum^{19, 20} which confirms the planar structure. The structures, which had been suggested by Oddo²¹ and Königs²² (2 and 3, and 4 and 5, respectively) to explain ambiguities in the reactions of pyrrole, were



also excluded by the spectroscopic data. Structures 6 and 7, which were originally proposed^{23, 24} to account for the unusual stability and the aromatic character of the pyrrole ring, were based upon Armstrong's centric structure²⁵ and Thiele's structure²⁶ for benzene.

Schomaker and Pauling's electron diffraction studies²⁷ gave approximate values to the bond angles and bond lengths of pyrrole. The microwave rotational spectrum gave more accurate dimensions and also confirmed the planarity of the molecule. The data indicated

¹⁹ W. S. Wilcox and J. H. Goldstein, *J. Chem. Phys.* **20**, 1656 (1952).

²⁰ B. Bak, D. Christensen, L. Hansen, and J. Rastrup-Andersen, *J. Chem. Phys.* **24**, 720 (1956).

²¹ B. Oddo, *Gazz. Chim. Ital.* **37**, 83 (1907); **52**, 42 and 56 (1922); **55**, 174 (1925); **61**, 699 (1931); **64**, 584 (1934).

²² W. J. Königs, *J. Prakt. Chem.* [2], **84**, 194 (1911).

²³ E. Bamberger, *Chem. Ber.* **24**, 1758 (1891).

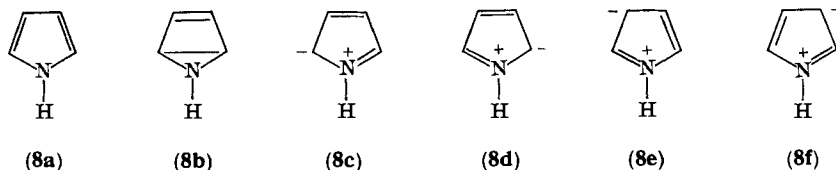
²⁴ G. L. Ciamician, *Chem. Ber.* **37**, 4200 (1904).

²⁵ H. E. Armstrong, *J. Chem. Soc.* **51**, 258 (1887).

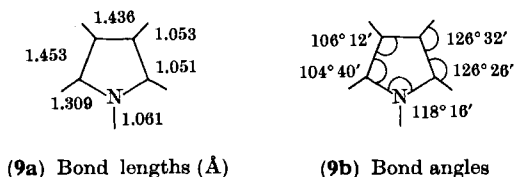
²⁶ J. Thiele, *Ann. Chem.* **306**, 87 (1899).

²⁷ V. Schomaker and L. Pauling, *J. Am. Chem. Soc.* **61**, 1769 (1939).

that the C-2-C-3 bond is not a simple double bond, thereby supporting the resonance hybrid nature of the pyrrole molecule (8) in which the electron pair on the nitrogen atom is incorporated in the aromatic sextet.



The size and direction of the dipole moment provide further evidence for delocalization of the electron pair. The structural data given in 9a and b are the most recent values calculated from the rotational spectrum.²⁸ Structural and microwave spectroscopic data have also been reported for 1-methylpyrrole.^{29, 30}



The general aromatic character of pyrrole³¹ and its extremely facile reaction with electrophiles^{6, 32} are readily rationalized in terms of the resonance hybrid. Values for the empirical resonance energy,³³⁻⁴³ which vary from 14.0 to 31.0 kcal/mole have been calculated from experimental heat of combustion data. Although there is some divergence in the experimental values for the resonance energy of

²⁸ C. W. N. Cumper, *Trans. Faraday Soc.* **54**, 1266 (1958).

²⁹ L. V. Vilkov, P. A. Akishin, and V. M. Presnyakova, *Zh. Strukt. Khim.* **3**, 5 (1962); *Chem. Abstr.* **58**, 7455 (1963).

³⁰ W. Arnold, H. Dreizler, and H. D. Rudolf, *Z. Naturforsch.* **23a**, 301 (1968).

³¹ Balaban^{31a} has assigned values of -26 and -77 for the aromaticity constants for pyrrole and the pyrrolyl anion, respectively (benzene = 0).

^{31a} A. T. Balaban and Z. Simon, *Tetrahedron* **18**, 315 (1962).

³² S. Clementi, F. Genel, and G. Marino, *Chem. Commun.* 498 (1968); P. Linda and G. Marino, *ibid.* 499 (1968).

³³ G. E. Coates and L. E. Sutton, *J. Chem. Soc.* 187 (1948).

³⁴ R. Klages, *Chem. Ber.* **82**, 358 (1949).

TABLE I
SELECTED PHYSICAL CONSTANTS FOR PYRROLE

Property	Value
Boiling point	130°/760 mm
Melting point	-18.5°
Critical temperature	366°
Density at 20°	0.96976
Refractive index at 15°	1.5105
Dielectric constant at 20°	8.00

pyrrole, comparative studies indicate that it is intermediate between those for furan and thiophene, the latter having the higher resonance energy. This order of aromatic character is supported by NMR-induced ring current measurements (see Section III, B, 3, a). Several comprehensive reviews⁴⁴⁻⁵¹ of other chemical thermodynamic properties have been published for pyrrole and a selection of the more important constants is recorded in Table I. Thermochemical data are also available for several polysubstituted pyrroles.^{44, 45}

³⁵ J. L. Franklin, *J. Am. Chem. Soc.* **72**, 4278 (1950).

³⁶ H. Grasshof, *Chem. Ber.* **84**, 916 (1951).

³⁷ S. Nagakura and T. Hosoya, *Bull. Chem. Soc. Japan* **25**, 179 (1952).

³⁸ G. W. Wheland, "Resonance in Organic Chemistry." Wiley, New York, 1955.

³⁹ L. Pauling, "The Nature of the Chemical Bond." Cornell Univ. Press, New York, 1960.

⁴⁰ C. A. Coulson, "Valence." Oxford Univ. Press, London and New York, 1961.

⁴¹ A. J. Owen, *Tetrahedron* **14**, 237 (1961).

⁴² H. Zimmermann and H. Geisenfelder, *Z. Elektrochem.* **65**, 368 (1961).

⁴³ J. D. Cox, *Tetrahedron* **19**, 1175 (1963).

⁴⁴ P. Rothmund and H. Beyer, *Ann. Chem.* **492**, 292 (1932).

⁴⁵ A. Stern and G. Klebs, *Ann. Chem.* **500**, 91 (1932).

⁴⁶ G. Milazzo, *Boll. Sci. Fac. Chim. Ind. Bologna* **94** (1941); *Chem. Abstr.* **37**, 2982 (1943).

⁴⁷ A. Marinangeli, *Ann. Chim. (Rome)* **44**, 211 (1954).

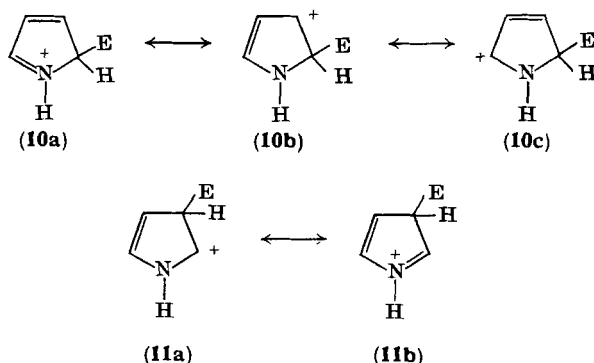
⁴⁸ J. Timmermans and H. Roland, *J. Chim. Phys.* **52**, 223 (1955).

⁴⁹ R. Blinc and J. Pahor, "J. Stefan" *Inst. Rept. (Ljubljana)* **4**, 123 (1957); *Chem. Abstr.* **53**, 41 (1959).

⁵⁰ D. C.-H. Cheng, J. C. McCoubrey, and D. G. Phillips, *Trans. Faraday Soc.*, **58**, 224 (1962).

⁵¹ D. W. Scott, W. T. Berg, I. A. Hossenlopp, W. N. Hubbard, J. F. Messerly, S. S. Todd, D. R. Douslin, J. P. McCullough, and G. Waddington, *J. Phys. Chem.* **71**, 2263 (1967).

The increased nucleophilic character of pyrrole, compared with benzene,^{32, 52} may be rationalized in terms of the π -electron excessive nature of the aromatic system, but, although the polar canonical structures (8c-f) indicate high electron densities in the α - and β -positions, one cannot predict the relative reactivities of these positions with electrophiles by simple inspection. Calculations⁵³ based upon the relationship between bond length and the number of π electrons in the bond suggest the following contributions of the canonical forms to the resonance hybrid: classic structure (8a), 62%; "Dewar" structure (8b), 1%; α -polar structure (8c and 8d), 29%; β -polar structure (8e and 8f), 8%. Consideration of the relative stabilities of the σ -transition complexes (10a-c and 11a, b) indicates the site of preferential electrophilic substitution to be the α -position. This deduction is in accord with the majority of the experimental observations,⁶ anomalous preferential β -substitution occurring only with nitrosation¹ and selenocyanation.⁵⁴



Over the past 20 years and, in particular since 1955, many theoretical studies of the electronic structure of pyrrole using the molecular orbital approach with varying degrees of refinement have been reported. The π -electronic structure of pyrrole has been extensively discussed in terms of both the simple Hückel molecular orbital (LCAO) theory^{37, 41, 55-65} and the more sophisticated self-consistent field molecular orbital method (SCFMO method).^{18, 66-77} Extended

⁵² D. N. Kursanov, M. E. Vol'pin, and Z. N. Parnes, *Khim. Nauka i Promy.* **3**, 159 (1958); *Chem. Abstr.* **52**, 20109 (1958).

⁵³ B. Bak, *Acta Chem. Scand.* **9**, 1355 (1955).

⁵⁴ L.-B. Agenäs and B. Lindgren, *Arkiv Kemi* **28**, 145 (1968).

Hückel calculations,^{78, 79} the generalized free electron (G-FEMO) method,^{48, 80} and the iterative ω and ω' techniques⁸¹⁻⁸³ have also been used.

In molecular orbital calculations of systems containing heteroatoms appropriate changes have to be made in the empirical Coulomb (α) and resonance (β) integrals associated with the heteroatom and the carbon-heteroatom bonds. The parameters are described in terms of

⁵⁵ H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* **43**, 87 (1947).

⁵⁶ L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

⁵⁷ E. Gyöerffy, *Compt. Rend.* **232**, 515 (1951).

⁵⁸ P. Chiorboli and P. Manaresi, *Gazz. Chim. Ital.* **84**, 248 (1954).

⁵⁹ S. S. Perez, M. A. Hevraez, F. J. Igea, and J. Esteve, *Anales Real. Soc. Españ. Fis. Quim. (Madrid)* **B51**, 91 (1955); *Chem. Abstr.* **49**, 8642 (1955).

⁶⁰ R. D. Brown, *Australian J. Chem.* **8**, 100 (1955).

⁶¹ R. D. Brown and B. A. Collier, *Australian J. Chem.* **12**, 152 (1959).

⁶² A. Julg and P. Carles, *J. Chim. Phys.* **59**, 852 (1962).

⁶³ P. Carles, *Compt. Rend.* **254**, 677 (1962).

⁶⁴ A. Julg, *Tetrahedron* **19**, Suppl. 2, 25 (1963).

⁶⁵ R. D. Brown, B. A. Collier, and M. L. Heffernan, *Tetrahedron* **18**, 343 (1962).

⁶⁶ J. A. Pople and P. Schofield, *Proc. Roy. Soc. A* **233**, 241 (1956).

⁶⁷ S. Carra and S. Polezzo, *Gazz. Chim. Ital.* **88**, 1103 (1958).

⁶⁸ R. D. Brown and M. L. Heffernan, *Australian J. Chem.* **12**, 319 (1959).

^{68a} R. D. Brown and M. L. Heffernan, *Australian J. Chem.* **12**, 330 (1959).

⁶⁹ R. L. Miller, P. G. Lykos, and H. N. Schmeising, *J. Am. Chem. Soc.* **84**, 4623 (1962).

⁷⁰ G. Leroy, *J. Chim. Phys.* **60**, 1270 (1963).

⁷¹ N. Solony, F. W. Birss, and J. B. Greenshields, *Can. J. Chem.* **43**, 1569 (1965).

⁷² M. D. Newton, F. P. Boer, and W. N. Lippcomb, *J. Am. Chem. Soc.* **88**, 2367 (1966).

⁷³ P. Chiorboli, A. Rastelli, and F. Monicchioli, *Theoret. Chim. Acta* **5**, 1 (1966).

⁷⁴ P. J. Black, R. D. Brown, and M. L. Heffernan, *Australian J. Chem.* **20**, 1325 (1967).

⁷⁵ A. Julg and P. Carles, *Theoret. Chim. Acta* **7**, 103 (1967).

⁷⁶ D. T. Clark, *Tetrahedron* **24**, 4689 (1968).

⁷⁷ R. L. Flurry and J. J. Bell, *Theoret. Chim. Acta* **10**, 1 (1968).

⁷⁸ W. Adam, A. Grimson, and G. Rodrigues, *Tetrahedron* **23**, 2513 (1967).

⁷⁹ R. B. Hermann, *Intern. J. Quantum Chem.* **2**, 165 (1968).

⁸⁰ W. Woznicki and B. Zurawski, *Acta Phys Polon.* **31**, 95 (1967). *Chem. Abstr.* **67**, 90327 (1967).

⁸¹ A. Streitwieser, *U.S. Dept. Comm., Office Tech. Serv. PB Rept.* **144,168** (1959); *Chem. Abstr.* **55**, 17195 (1961); *J. Am. Chem. Soc.* **52**, 4123 (1960).

⁸² M. Scholz and D. Heidrich, *Monatsh. Chem.* **98**, 254 (1967); D. Heidrich and M. Scholz, *ibid.* 264.

⁸³ S. Ehrenson, *J. Phys. Chem.* **66**, 706 (1962).

the standard Coulomb (α_C) and resonance (β_{CC}) integrals by the following relationships:

$$\begin{aligned}\alpha_N &= \alpha_C + h_N \beta_{CC} \\ \beta_{CN} &= K_{CN} \beta_{CC}\end{aligned}$$

Difficulties in the choice of appropriate values for the constants h_N and K_{CN} have led to the divergence in the calculated results of π -electron densities and orbital energies by different workers and there has been much discussion concerning the factors influencing such parameters.^{77, 84-86}

The constant h is positive for atoms that have a greater electron affinity than carbon and negative for those atoms whose electron affinity is less than carbon. For pyrrole, values of from 0.6 to 2.0 have been used for h_N .⁸⁷ It has been suggested that the value of K is a simple function of bond distance,⁸⁸ but this method for its calculation has little theoretical foundation. If the relationship is accepted, then K_{CN} for pyrrole would be *ca.* 0.84, but the values for K_{CN} which give the best agreement between theoretical and experimental data lie in the range 0.9-1.1.⁸⁷ The critical dependence of the charge density on both α_N and β_{CN} illustrates the importance in the correct choice of h_N and K_{CN} .⁷⁷ Another factor which complicates the Hückel MO calculations is the so-called auxiliary inductive parameter (h_i), which is assigned to the carbon atoms adjacent to the heteroatom. The use of h_i has been both criticized⁸⁹ and justified.^{65, 90} Calculations of π -electron densities for the α - and β -positions (Table II) neglecting h_i suggest that the β -position would be the more reactive site for electrophilic substitution. Atom localization energies indicate the reverse order of reactivity. If electrophilic substitution involves a transition state in which bond formation is well developed, then the controlling factor is the atom localization energies; whereas, if the transition state involves little bonding, the reaction process is controlled by the π -electron densities.

⁸⁴ A. Lofthus, *Mol. Phys.* **2**, 367 (1959).

⁸⁵ F. L. Pilar and J. R. Morris, *J. Chem. Phys.* **34**, 389 (1961).

⁸⁶ R. D. Brown and A. Penfold, *Trans. Faraday Soc.* **53**, 397 (1957).

⁸⁷ A. Streitwieser, "Molecular Orbital Theory for Organic Chemists." Wiley, New York, 1961.

⁸⁸ C. Sandorfy, *Bull. Soc. Chim. France* 615 (1949).

⁸⁹ R. McWeeny, *Proc. Roy. Soc. A* **237**, 355 (1956).

⁹⁰ M. J. S. Dewar [*J. Chem. Soc.* 463 (1949)] has proposed that the specific origin of the auxiliary inductive effect lies in the ionic character of the σ bond between the heteroatom and its adjacent carbon atom.

TABLE II
SELECTED VALUES OF THE CALCULATED
 π -ELECTRON DISTRIBUTION IN PYRROLE

N	α	β	Ref.
1.806	1.046	1.051	70
1.784	1.045	1.063	75
1.732	1.016	1.118	66
1.700	1.080	1.070	41
1.636	1.072	1.110	67
1.640	1.153	1.027	68
1.628	1.146	1.040	53
1.620	1.090	1.100	56
1.430	1.115	1.170	57

In view of the highly reactive character of pyrrole, the controlling factor for electrophilic substitution is considered to be the π -electron densities. To obtain an agreement between Hückel MO calculations and experimental observations of chemical reactivity, recourse has to be made to the use of the auxiliary inductive parameter. Satisfactory results are obtained when $h = 2$ and $h_i = 0.25$.

An alternative approach involves the calculation of "frontier electron densities."^{91, 92} The relative reactivities of the α - and β -positions with electrophiles are considered to be governed only by the π -electron density in the highest occupied energy level. Although such a procedure has been criticized,⁹³⁻⁹⁵ it has been developed for heterocyclic systems and its interpretation has been shown to depend not only on the highest occupied energy level of the nucleophilic centers on the heterocyclic ring but also on the lowest unoccupied energy level of the attacking electrophile.⁹⁶ Frontier electron densities have been calculated by two groups of workers to be 0.76628⁶⁷ or 0.344⁶⁹ for the α -position and 0.23372⁶⁷ or 0.156⁶⁹ for the β -position.

⁹¹ K. Fukui, T. Yonezawa, and H. Shingu, *J. Chem. Phys.* **20**, 722 (1952).

⁹² K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.* **22**, 1433 (1954).

⁹³ B. Pullman, *J. Chem. Phys.* **31**, 551 (1959).

⁹⁴ H. H. Greenwood, *J. Chem. Phys.* **20**, 1653 (1952); **23**, 756 (1955); **31**, 552 (1959).

⁹⁵ S. S. Sung, O. Chalvet, and R. Dandel, *J. Chem. Phys.* **31**, 553 (1959).

⁹⁶ G. Klopman, *J. Am. Chem. Soc.* **90**, 223 (1968).

Although the values differ considerably for the two calculations, the relative sizes of the electron densities for the α - and β -positions are approximately the same and lead to the prediction of preferential electrophilic substitution in the α -position.

The somewhat arbitrary use of the auxiliary inductive parameter in the Hückel MO calculations has been questioned and the effect of the nonuniform distribution of σ -electron densities, particularly in the CN bond,⁹⁰ upon the π -electron distribution has been discussed.⁶⁵ Variable electronegativity self-consistent field (VESCF) molecular orbital calculations, which are an elaboration of the conventional SCF method and allow for the variation in electronegativity of an

TABLE III
TOTAL σ - AND π -ELECTRON DISTRIBUTION IN
PYRROLE

	N	α	β	Ref.
σ	3.5629	2.8377	3.0026	76
π	1.6553	1.0848	1.0854	
σ	3.7448	3.0302	3.1602	18
π	1.6589	1.0752	1.0953	
σ	—	2.8200	3.0300	78
π	—	1.0800	1.1300	

atom with its charge density, give a π -electron distribution which is consistent with the orientation of electrophilic substitution of pyrrole and also gives orbital energies in fair agreement for the observed electronic transition energies.⁶⁸ As the polarized σ -electron system of the pyrrole ring will certainly affect the π -electron distribution, it is becoming increasingly obvious that one cannot completely ignore the σ electrons and several SCFMO calculations including all valence electrons have been reported.^{18, 76, 78, 79} The resultant electron distributions (Table III), however, are very close to those calculated by other methods. It has been shown that when all the valence electrons were considered, then although a close correlation between the observed NMR chemical shifts of the α - and β -protons and the values calculated from the π -electron densities was obtained, the charge densities were not related to the electrophilic reactivity.⁷⁹

Although MO calculations do give an indication of the relative reactivity of the α - and β -positions, no satisfactory explanation has been proposed for the relatively unreactive character of the nitrogen atom. In all theoretical calculations, the charge density on the nitrogen atom is considerably higher than on the carbon atoms. This anomaly may only be explained when we have more detailed information on the mechanism of pyrrole substitution reactions.

Under alkaline conditions, the pyrrolyl anion may be the reactive species involved in substitution. Several MO calculations have been made for the anion.^{68a, 76, 78} The relative electronegative parameter h_N is negative. Brown's VESCF MO method^{68a} gives an equidistribution of the π electrons throughout the ring, whereas the calculations made by Clark⁷⁶ and Adam *et al.*⁷⁸ indicate that most of the negative charge remains localized on the nitrogen atom and that the charge density at the β -position is higher than at the α -position. A comparison of the results of Adam's extended Hückel MO calculations for pyrrole and its anion, however, shows a somewhat unrealistic equality of the π -electron distribution for the two systems. An evaluation of the Coulombic integrals for the conjugate acid of pyrrole has been attempted, but unfortunately an incorrect structural model was used.⁵⁷

Molecular orbital calculations have also been made for carbonyl derivatives of pyrrole^{97, 98} and for 2-phenylpyrrole.⁹⁹

The valence bond method has not been used as widely as the molecular orbital approach. With the inclusion of polar structures, however, the valence bond method gives correct orientation for electrophilic substitution and a calculated dipole moment close to the experimental value.¹⁰⁰ An application of the one-center method of the π -electron system of pyrrole gives electron densities of 1.612, 1.167, and 1.028 on the nitrogen atom and the α - and β -carbon atoms, respectively.¹⁰¹ Transition energies and the dipole moment by this method are in accord with the observed values.

⁹⁷ P. Chiorboli, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **12**, 713 (1952); *Chem. Abstr.* **47**, 3683 (1953).

⁹⁸ P. Chiorboli and P. Manaresi, *Gazz. Chim. Ital.* **83**, 114 (1953).

⁹⁹ V. I. Minkin, A. F. Pozharskii, and Yu. A. Ostroumov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* p. 551 (1966); *Chem. Abstr.* **66**, 10481 (1967).

¹⁰⁰ M. Simmonetta, *J. Chim. Phys.* **49**, 68 (1952).

¹⁰¹ H. Hartmann and K. Jug, *Theoret. Chim. Acta* **3**, 439 (1965).

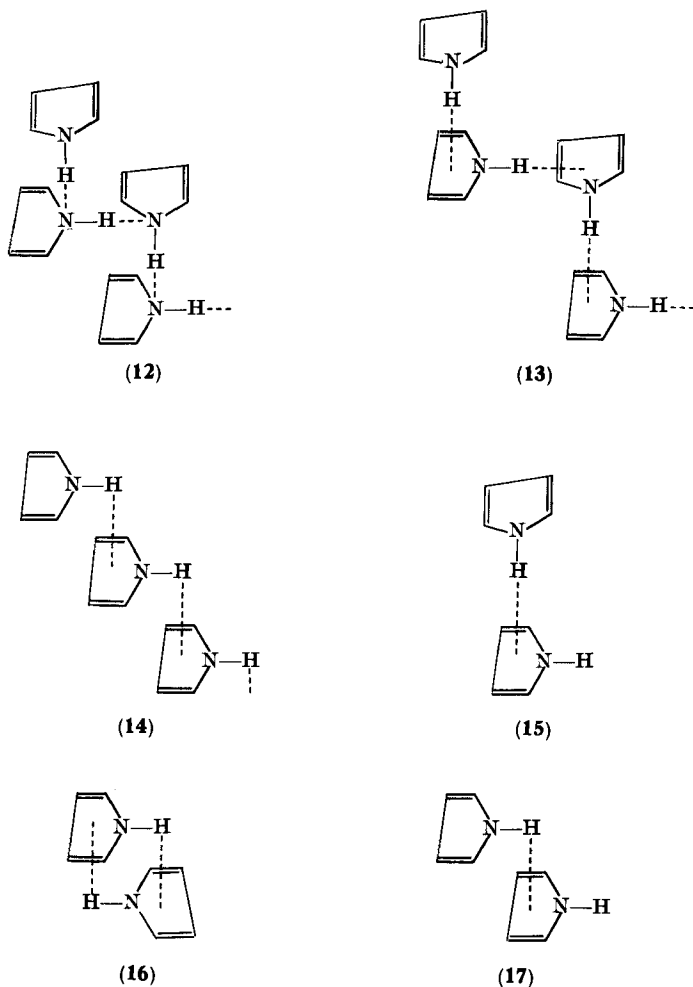
B. MOLECULAR ASSOCIATION

1. *NH- π Bonding*

a. *Autoassociation.* Many of the physical characteristics of pyrrole are not compatible with a monomolecular structure. In particular, the boiling point, 130° – 131° /761 mm, is considerably higher than that of furan, 32° /758 mm, and is more comparable with that of 1-ethylpyrrole, 129° – 130° /762 mm, indicating some form of association. The exact nature of the association has been the subject of many investigations^{47, 102–121} and several models have been postulated (12–17).

The NH-stretching frequency of pyrrole, measured for a dilute solution in carbon tetrachloride,^{102–104} appears as a doublet and the

- ¹⁰² P. Mirone, *Atti Accad. Nazl. Lincei. Rend., Classe Sci. Fis., Mat. Nat.* [8] **11**, 365 (1951); *Chem. Abstr.* **48**, 8049 (1954).
¹⁰³ N. Fuson, M. L. Josien, R. L. Powell, and E. Utterback, *J. Chem. Phys.* **20**, 145 (1952).
¹⁰⁴ P. Mirone and M. Vampari, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **12**, 405 (1952); *Chem. Abstr.* **47**, 404 (1953).
¹⁰⁵ M. L. Josien and N. Fuson, *J. Chem. Phys.* **22**, 1169 and 1264 (1954).
¹⁰⁶ P. Chiorboli and P. Manaresi, *Gazz. Chim. Ital.* **84**, 269 (1954).
¹⁰⁷ P. Mirone, *Gazz. Chim. Ital.* **86**, 165 (1956).
^{107a} P. Mirone and G. Fabbri, *Gazz. Chim. Ital.* **86**, 1079 (1956).
¹⁰⁸ P. Toumikoski, *Suomen Kemistilehti* **B23**, 44 (1950); *Chem. Abstr.* **45**, 38 (1951).
¹⁰⁹ P. Toumikoski, *J. Chem. Phys.* **20**, 1054 (1952); **22**, 2096 (1954).
¹¹⁰ P. Toumikoski, *J. Phys. Radium* **15**, 318 (1954); **16**, 347 (1955).
¹¹¹ P. Toumikoski, *Mikrochim. Acta* p. 505 (1955).
¹¹² M. L. Josien, M. Paty, and P. Pineau, *Compt. Rend.* **241**, 199 (1955).
^{112a} M. L. Josien, M. Paty, and P. Pineau, *J. Chem. Phys.* **24**, 1261 (1956).
¹¹³ R. H. Linnell, *J. Chem. Phys.* **21**, 179 (1953).
¹¹⁴ S. N. Vinogradov and R. H. Linnell, *J. Chem. Phys.* **23**, 93 (1955).
¹¹⁵ L. Jannelli and P. Orsini, *Rend. Accad. Sci. Fis. Mat. (Soc. Nazl. Sci., Napoli)* [4] **26**, 246 (1959); *Chem. Abstr.* **58**, 12003 (1963).
¹¹⁶ R. K. Hind, E. McLaughlin, and A. R. Ubbelohde, *Trans. Faraday Soc.* **56**, 331 (1960).
¹¹⁷ M. Gomel and H. Lumbroso, *Compt. Rend.* **252**, 3039 (1961).
^{117a} M. Gomel and H. Lumbroso, *Bull. Soc. Chim. France* 2200 (1962).
^{117b} M. Gomel and H. Lumbroso, *Bull. Soc. Chim. France* 2206 (1962).
^{117c} M. Gomel and H. Lumbroso, *Bull. Soc. Chim. France* 2212 (1962).
¹¹⁸ G. M. Badger, R. L. N. Harris, R. A. Jones, and J. M. Sasse, *J. Chem. Soc.* p. 4329 (1962).
¹¹⁹ J. A. Happe, *J. Phys. Chem.* **65**, 72 (1961).
¹²⁰ V. Lorenzelli and A. Alemagna, *Compt. Rend.* **257**, 2977 (1963).
¹²¹ V. Lorenzelli and G. Randi, *Atti Acad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **36**, 646 (1964); *Chem. Abstr.* **62**, 7612 (1965).



intensities of the two bands depend upon the concentration of pyrrole (Fig. 1). The higher frequency band was assigned to the "free" non-bonded NH-stretching vibration and the lower frequency band was ascribed to an NH-N bonded NH vibration. These results were further supported by the Raman spectrum.^{104, 106} It was postulated that the association could be described as a chain polymer (12).^{102, 103} This type of association was questioned by Tuomikoski,¹⁰⁹ who measured the dielectric constant of pyrrole over a wide temperature range. He suggested that the correlation of the dipole moment of pyrrole with

its dielectric constant indicated that the autoassociation of pyrrole did not involve NH-N bonds and he interpreted his dielectric constant and IR data¹⁰⁸⁻¹¹¹ in terms of head-to-head dimerization resulting from dipole-dipole interaction. The existence of dimers rather than polymers was also postulated by Marinangeli.⁴⁷ Josien *et al.*,^{112a} however, presented results of their cryoscopic studies of pyrrole in cyclohexane which they interpreted as indicating that the association did not stop at the dimeric stage but was polymeric. They also considered

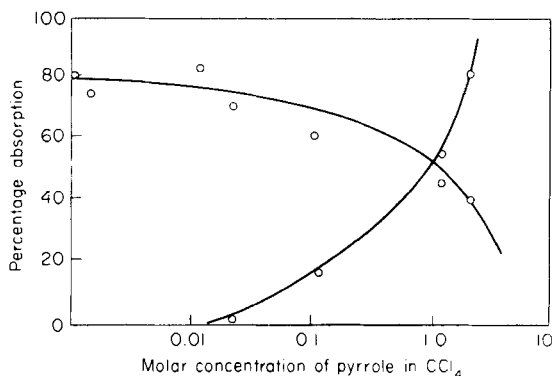


Fig. 1. The intensities of bonded and nonbonded ν_{NH} absorption bands in CCl_4 .

that a polymer of type **12** enables one to account for the direction in variation of the dielectric constant with temperature. Data from a cryoscopic study of pyrrole in benzene suggested only dimeric association of the pyrrole molecules.¹¹⁵ Such a system, however, is complicated by the possibility of association between the solvent and solute (*vide infra*). A comparison of the dipole moments of pyrrole and 1-methylpyrrole in the gas and liquid phase and in several non-polar solvents led Gomel and Lumbroso^{117, 117a} to the conclusion that the dimer had a cyclic NH- π -bonded structure (**16**), whereas a comparative study of the NH stretching frequency of pyrrole in carbon tetrachloride containing varying concentrations of 1-substituted pyrroles indicated an "open" NH- π -bonded dimer of type **15** or **17**.¹¹⁸ These general conclusions that the preferred autoassociation of pyrrole in solution is a dimeric NH- π -bonded structure are supported by NMR spectroscopy^{119, 122} (Section III, B, 3), which favors the

¹²² M. T. Chenon and N. Lumbroso-Bader, *Compt. Rend.* **266**, 293 (1968).

"closed" dimeric model, but does not rigorously exclude the "open" dimer.¹¹⁹ Low-frequency IR studies of pyrrole^{120, 121} in the liquid phase reveal an absorption band at 110 cm^{-1} which cannot be assigned to a fundamental vibration of the molecule.¹²³ The intensity of the band does not follow the Beer-Lambert law and it has been assigned to the $\text{NH}-\pi$ vibration. The changes in intensity suggest polymeric association in the liquid phase but a closed dimeric structure in solution.

b. *Association with π Donors.* The effect of a change of solvent on the spectroscopic properties of pyrrole has been extensively studied.^{105, 106, 119, 122, 124-153} The pyrrole molecule can act either as a

¹²³ R. C. Lord and F. A. Miller, *J. Chem. Phys.* **10**, 328 (1942).

¹²⁴ A. M. Buswell, J. R. Downing, and W. H. Rodebush, *J. Am. Chem. Soc.* **61**, 3252 (1939).

¹²⁵ V. M. Zezyulinskii, *Zh. Fiz. Khim.* **24**, 1442 (1950); *Chem. Abstr.* **45**, 4558 (1951).

¹²⁶ M. L. Josien and P. Dizabo, *Compt. Rend.* **243**, 44 (1956).

¹²⁷ L. W. Reeves, *Can. J. Chem.* **35**, 1351 (1957).

¹²⁸ N. Fuson, P. Pineau, and M. L. Josien, *Hydrogen Bonding, Papers Symp. Ljubljana*, 1957 p. 169. Pergamon Press, Oxford, 1959; *Chem. Abstr.* **55**, 1185 (1961).

^{128a} N. Fuson, P. Pineau, and M. L. Josien, *J. Chim. Phys.* **55**, 454 and 464 (1958).

¹²⁹ M. L. Josien and G. Sourisseau, *Hydrogen Bonding, Papers Symp. Ljubljana*, 1957 p. 129. Pergamon Press, Oxford, 1959.

¹³⁰ L. J. Bellamy, H. E. Hallam, and R. L. Williams, *Trans. Faraday Soc.* **54**, 1120 (1958).

¹³¹ J. P. Leickman, J. Lascombe, N. Fuson, and M. L. Josien, *Proc. 4th Intern. Meeting Mol. Spectry., Bologna*, 1958 Vol. 2, p. 858 (1959); *Chem. Abstr.* **59**, 4683 (1963).

^{131a} J. P. Leickman, J. Lascombe, N. Fuson, and M. L. Josien, *Bull. Soc. Chim. France* 1516 (1959).

¹³² L. J. Bellamy and H. E. Hallam, *Trans. Faraday Soc.* **55**, 220 (1959).

¹³³ M. L. Josien and J. Lascombe, *Collog. Intern. Centre Natl. Rech. Sci. (Paris)* **77**, 137 (1959); *Chem. Abstr.* **54**, 2936 (1960).

¹³⁴ R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **37**, 1056 (1959).

¹³⁵ R. Freymann, M. Freymann, M. Koechlin, M. Martin, and M. G. Mavei, *Arch. Sci. (Geneva)* **12**, 207 (1959); *Chem. Abstr.* **54**, 11705 (1960).

¹³⁶ M. Freymann and R. Freymann, *Compt. Rend.* **248**, 677 (1959).

¹³⁷ W. C. Price, W. F. Shermann, and G. R. Wilkinson, *Proc. Roy. Soc. A* **255**, 5 (1960).

¹³⁸ L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc. A* **255**, 22 (1960).

¹³⁹ T. P. Schaefer and W. G. Schneider, *J. Chem. Phys.* **32**, 1224 (1960).

¹⁴⁰ C. Giessner-Piette, *Compt. Rend.* **250**, 2547 (1960).

¹⁴¹ Z. Pajak, *Arch. Sci. (Geneva)* **13**, 527 (1960); *Chem. Abstr.* **57**, 16523 (1962).

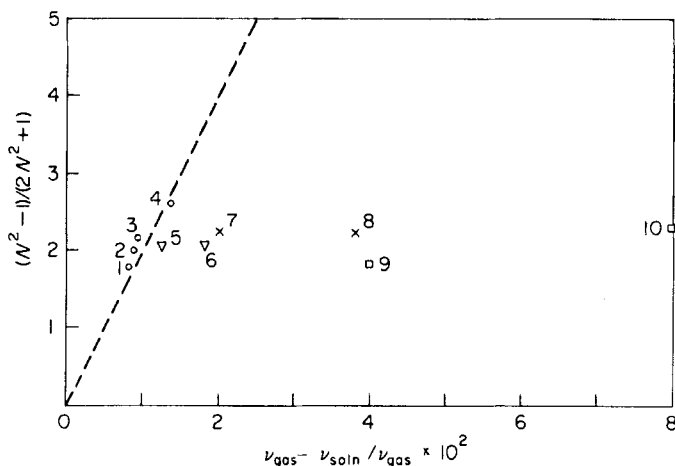


FIG. 2. Kirkwood-Bauer-Magat plot for ν_{NH} . Nonpolar solvents (○): 1, hexane; 2, cyclohexane; 3, carbon tetrachloride; and 4, carbon disulfide. Polar solvents (▽): 5, chloroform and 6, 1,2-dichloroethane. π -H Bonding solvents (×): 7, benzene and 8, liquid pyrrole. X-H Bonding solvents (□): 9, acetone and 10, pyridine.

proton donor forming NH-X or NH- π hydrogen bonds, or as a proton acceptor to form π -H-X hydrogen bonds. Association can also occur via dipole-dipole or π -dipole interactions. In nonpolar solvents there is little or no association between pyrrole and the solvent, as shown by the correlation between the frequency shift of the NH-stretching

- ¹⁴² Z. Pajak and F. Pellon, *Compt. Rend.* **251**, 79 (1961).
- ¹⁴³ P. V. Huong, J. Lascombe, and M. L. Josien, *J. Chim. Phys.* **58**, 694 (1961).
- ¹⁴⁴ M. Gomel and P. Pineau, *Compt. Rend.* **252**, 2870 (1961).
- ¹⁴⁵ L. Denolin-Dewaersegge and G. van Binst, *Bull. Soc. Chim. Belges* **71**, 615 (1962).
- ¹⁴⁶ S. S. Mitra, *J. Chem. Phys.* **36**, 3286 (1962).
- ¹⁴⁷ L. J. Bellamy and R. J. Pace, *Spectrochim. Acta* **19**, 1831 (1963).
- ¹⁴⁸ A. A. Petrov, N. V. Elsakov, and U. B. Lebedev, *Opt. i Spektroskopiya* **17**, 679 (1964); *Chem. Abstr.* **62**, 12626 (1965).
- ¹⁴⁹ J. A. Pullin and R. L. Werner, *Spectrochim. Acta* **21**, 1257 (1965).
- ¹⁵⁰ G. Randi and F. Gesmundo, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **40**, 95 (1966); *Chem. Abstr.* **65**, 11552 (1966).
- ¹⁵¹ J. Royane and D. H. Williams, *J. Chem. Soc., B* p. 805 (1967).
- ¹⁵² T. Ledaal, *Tetrahedron Letters* p. 1683 (1968).
- ¹⁵³ D. M. Porter and W. S. Brey, *J. Phys. Chem.* **72**, 650 (1968).
- ¹⁵⁴ W. West and R. T. Edwards, *J. Chem. Phys.* **5**, 14 (1937).
- ^{154a} E. Bauer and M. Magat, *J. Phys. Radium* **9**, 319 (1938).

vibration, relative to that observed in the gaseous phase, and the value predicted from the Kirkwood-Bauer-Magat relationship.^{154, 154a} Association between pyrrole and the solvent produces deviations from the expected value and the deviations are particularly large when the interaction involves a hydrogen bond of the type NH-X (Fig. 2).

As is seen from the previous section, autoassociation of pyrrole involves NH- π bonding. Hydrogen bonding of this type can also occur between pyrrole and other aromatic σ and π -electron systems. The strength of such bonds is less than that of the pyrrole dimer and considerably smaller than observed for NH-X bonds (*vide infra*), as shown by the frequency shift of the NH stretching vibration (Table IV).

TABLE IV
FREQUENCY SHIFTS (cm^{-1}) OF THE NH STRETCHING VIBRATION FOR
DILUTE SOLUTIONS OF PYRROLE IN π -NH BONDING SOLVENTS

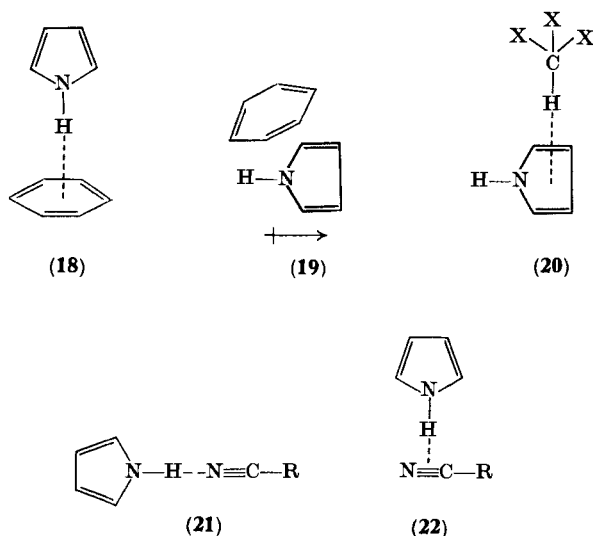
Solvent ^a	$\Delta\nu = \nu$ (free NH) - ν (bonded NH)
Benzene	26
Thiophene	32
Pyrrole	77
1-Alkylpyrroles	ca. 85
1-Alkyl-2,5-dimethylpyrroles	ca. 104
Alkyl cyanides	ca. 90

^a Solvent: CCl_4 plus ca. 1-5 M π donor.

The orientation of association of the benzene molecule about the pyrrole NH group is open to some conjecture. It was assumed from IR studies¹¹⁸ that the orientation was orthogonal (18). Such a model is also compatible with solvent-dependence studies of the molar Kerr constant.¹⁵⁵ The model does not, however, adequately account for the solvent effect of benzene upon NMR chemical shifts of the α - and β -protons of pyrrole (see Section III, B, 3, a). The NMR observations are best explained in terms of a nonplanar configuration (19) resulting not from NH- π bonding but, instead, from a π -dipole interaction.¹⁵¹ In an attempt to confirm the orthogonal model, LeFèvre *et al.*¹⁵⁵

¹⁵⁵ R. J. W. LeFèvre, D. V. Radford, G. L. D. Ritchie, and P. J. Stiles, *J. Chem. Soc., B* 148 (1968).

measured the Kerr constant for 1-methylpyrrole in benzene and carbon tetrachloride. As the values were the same in each solvent, it was deduced that the benzene-1-methylpyrrole complex had the non-planar configuration (19). The apparent contradictory evaluation of the Kerr constant data and the NMR data for the association of pyrrole and benzene has led to the suggestion that, in addition to the benzene molecule orthogonal to the NH bond, another one or two benzene rings are orientated at about 35° to the pyrrole molecule.¹⁵⁵ However, there appears to be no evidence to confirm that the pyrrole-benzene association is anything but a 1:1 complex.^{128a}



Pyrrole also acts as a π -electron donor in association with trihalomethanes to form weak 1:1 CH- π complexes (20).¹⁴¹ Similarly pyrrole appears to form (pyrrole) π -H-O bonds with phenol instead of an NH-O< hydrogen bond or NH- π (phenol) bonds.¹¹² The association between pyrrole and nitriles has been described both as NH-N¹³² (21) and as NH- π ^{146, 156} (22) hydrogen-bonded complexes. No definite conclusion has been reached but the NH frequency difference between the bonded and nonbonded vibration is more compatible with a NH- π -bonded model (Table IV).

¹⁵⁶ H. Lumbroso, *J. Chim. Phys.* **61**, 132 (1964).

2. *NH-X Bonding*

It has already been seen that hydrogen-bonded complexes which lie farthest from the Kirkwood-Bauer-Magat line are those in which the NH group is bonded to an atom having a high electron density and therefore capable of forming a strong NH-X hydrogen bond. The strongest bond is formed when the three atoms are colinear and hence the orientation of the complex is predictable. Confirmation of the orientation of association has been provided by dipole moment studies (see Section III, A, 2). The formation of the complexes has been investigated by IR^{114, 117, 124, 125, 128, 128a, 133, 144, 147, 149, 150, 156-158} and NMR^{119, 122, 153} spectroscopy and, in many cases, the association constant and the enthalpy of association have been determined.^{159, 159a}

The predominance of NH-X hydrogen bonding over other types of intermolecular association is readily distinguished by the large shift in the position of the NH stretching vibration to lower frequency (compare data in Tables IV and V). A linear correlation has been

TABLE V
FREQUENCY SHIFTS (cm^{-1}) ON THE NH STRETCHING VIBRATION FOR
DILUTE SOLUTIONS OF PYRROLE IN NH-X BONDING SOLVENTS

Solvent	$\Delta\nu = \nu \text{ (free NH)} - \nu \text{ (bonded NH)}$
Diethyl ether	141
Triphenylphosphine oxide	230
Pyridine	245
Triethylphosphine	270
Triethylamine	295

shown to exist between $\Delta\nu_{\text{XH}}$ and the basicity of Y in hydrogen-bonded systems of the general type XH-Y and this has also been found to be the case for molecular complexes involving the pyrrolyl NH group. It has been suggested that a better correlation is obtained between the pK_a of the proton acceptor and the association constant for the molecular complex formation.¹⁵⁷ This, however, appears to be correct only for systems in which steric interactions do not inhibit molecular

¹⁵⁷ T. Granstad and W. J. Fuglevik, *Spectrochim. Acta* **21**, 503 (1965).

¹⁵⁸ K. J. Morgan and N. Unwin, *J. Chem. Soc., B* 1336 (1967).

¹⁵⁹ H. J. Wimitte and R. H. Linnell, *J. Phys. Chem.* **66**, 546 (1962).

^{159a} F. Cruege, P. Pineau, and J. Lascombe, *J. Chim. Phys.* **64**, 1161 (1967).

complex formation. The strength of the NH–N bond for pyrrole–pyridine complexes, as given by $\Delta\nu_{\text{NH}}$, is related to the electron density on the pyridine nitrogen atom, as reflected in the $\text{p}K_a$ values of the pyridines. The ease of formation and the stability of the complex, however, are affected by the steric effects of the α, α' -substituents on the pyridine ring. Thus, although the basicity of 2,4,6-collidine is greater than that of 4-picoline, the association constants of the two compounds with pyrrole are relatively constant (Table VI).

TABLE VI
NH FREQUENCY SHIFTS($\Delta\nu_{\text{NH}}$) AND ASSOCIATION CONSTANTS
(K_{assoc}) FOR PYRROLE–PYRIDINE COMPLEXES AND $\text{p}K_a$ OF
THE ASSOCIATED PYRIDINE^a

Pyrrole complex	$\Delta\nu_{\text{NH}}$ (cm ⁻¹)	K_{assoc}	$\text{p}K_a$
Pyridine	245 ± 20	2.7 ± 3	5.30
4-Picoline	265 ± 15	4.1 ± 4	6.10
2,4,6-Collidine	300 ± 10	4.1 ± 4	7.63

^a $\text{p}K_a$ values determined potentiometrically in aqueous solution containing 10% ethanol [N. Ikekawa, Y. Sato, and T. Maeda, *Pharm. Bull. (Japan)* **2**, 205 (1954); *Chem. Abstr.* **50**, 994 (1956)].

A comparison of the dipole moments of pyrrole and of pyridine, 4-picoline, and 2,4,6-collidine with the resultant moments of the binary molecular complexes indicates that the NH–H-bonded complexes of pyrrole with pyridine and with 4-picoline are colinear, whereas this does not appear to be so for the pyrrole–collidine complex.^{117b} It was suggested that an alternative molecular interaction involving an NH– π bond similar to that postulated for the pyrrole–benzene system (*vide supra*) was operating.¹¹⁷ Such bonding, however, is extremely unlikely in view of the π -electron deficiency of the pyridine ring. Also, the large frequency shift of the pyrrole NH stretching vibration, which is observed on the formation of the pyrrole–collidine complex, is not indicative of NH– π bond formation. Both the IR and dipole moment data can be rationalized in terms of an NH–N-bonded complex in which the pyrrole nucleus is bent from the normal colinear configuration by steric interaction with the α -methyl groups of the collidine. There is, however, no conclusive evidence for such a configuration and further investigations are needed.

Viscosity,^{160, 160a} surface tension,¹⁶¹ and cryoscopic¹⁶² measurements have also been applied to the study of the pyrrole-pyridine complex.

Pyrrole forms weaker NH-O hydrogen-bonded complexes with ethers.^{106, 156, 157, 163} The dipole moment of the pyrrole-1,4-dioxane complex shows it to be predominantly a binary system in which the pyrrole molecule occupies an axial position to the dioxane ring¹⁶³ (see Section III, A, 2). Particularly strongly hydrogen-bonded NH-O=C complexes are formed between pyrrole and ketones.^{147, 149, 156} IR studies of the effect of the complex formation upon both the NH- and the C=O stretching frequencies have been made.

The general effect of NH-X hydrogen bonding on the NMR spectrum of pyrrole is to shift the α -proton resonance to lower field and to leave the β -proton resonance relatively unchanged from its position when the spectrum is measured in carbon tetrachloride. This effect should be compared with the characteristic upfield shift of the α -proton resonance and downfield shift of the β -proton resonance which results from the formation of NH- π complexes (see Section III, B, 3, a).

A comparison of the relative frequency shifts of the NH- and ND stretching vibrations of pyrrole and pyrrole-1-*d* in both polar and nonpolar solvents indicates that the stabilities of both ND- π and ND-X bonded complexes are less than for the corresponding NH complexes.^{131, 131a, 143} The isotope effect results from a difference in energies of the fundamental states of the ND and NH vibrators which is reflected in the energy differences of the double potential minimum of the hydrogen bond.¹⁴³

3. Molecular Association of Substituted Pyrroles

Dipole moment studies^{117a} of 1-methylpyrrole in the gas and liquid phases suggest that the compound exists as a dimeric complex in a similar spatial arrangement to that of the closed NH- π -bonded dimer of pyrrole (16). In the absence of the possibility of hydrogen bonding through a pyrrolyl NH group, the only remaining intermolecular association possible is via either π -dipole or dipole-dipole interactions.

¹⁶⁰ M. Dezelic, *Trans. Faraday Soc.* **33**, 713 (1937).

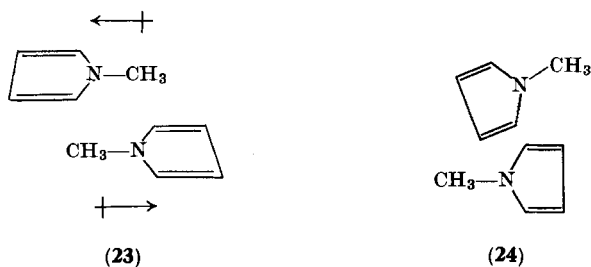
^{160a} M. Dezelic and B. Belia, *Ann. Chem.* **535**, 291 (1938).

¹⁶¹ N. Cagnoli, *Ann. Chim. (Rome)* **48**, 839 (1958).

¹⁶² P. Chiorboli and G. Morisi, *Gazz. Chim. Ital.* **84**, 1066 (1954).

¹⁶³ M. Veyret and M. Gomel, *Compt. Rend.* **258**, 4506 (1964).

The effect of change of solvent and of dilution upon the NMR spectrum of 1-methylpyrrole also provides supporting evidence of a dipole-dipole interaction between the molecules in the liquid phase.¹⁵¹ The 1-methyl and α -proton resonances move to lower field on dilution of a solution of the compound in carbon tetrachloride, whereas the β -proton resonance moves to higher field. Similar solvent-induced shifts are observed in the chemical shifts of the α - and β -protons of 1-*n*-butylpyrrole.¹³⁹ Anderson¹⁶⁴ has interpreted the dilution and solvent effects as indicating the presence of the closed dimer (23). The directions of the solvent-induced shifts, however, are not directly comparable with those observed for pyrrole under similar conditions¹¹⁹ and are more compatible with a structure similar to that described for the pyrrole-benzene system (24) involving a π -dipole interaction,¹⁵¹ but even this model does not adequately explain all the observations and the system may be more complex than a simple

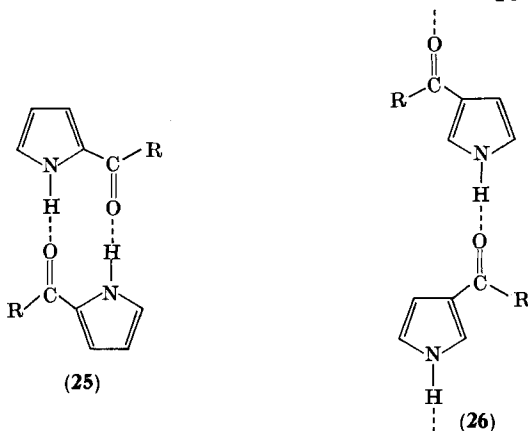


binary association. 1-Methylpyrrole also forms a nonplanar complex with benzene via a π -dipole interaction.^{151, 155}

Pyrroles having electron-withdrawing substituents in the β -position are usually less soluble in nonpolar solvents than are the corresponding α -substituted compounds. As the importance of the zwitterionic canonical form to the resonance hybrid is less for the β -isomers than for the α -substituted compounds, the lower solubility of the β -substituted pyrroles most probably results from a difference in the intermolecular association of the two compounds. Pyrroles that have carbonyl substituents in the α -position readily form dimeric complexes via $\text{NH}-\text{O}=\text{C}$ hydrogen bonds (25) in the liquid phase and in concentrated solution. The dimeric species may also exist in the solid phase and only in very dilute solutions ($< ca. 10^{-4} M$) do the com-

¹⁶⁴ H. J. Anderson, *Can. J. Chem.* **43**, 2387 (1965).

pounds exist in a monomeric state.^{165, 166, 166a} Numerous examples of this type of association have been investigated using cryoscopic^{167, 167a, 168} and ebullioscopic^{167, 167a} techniques and with spectroscopic¹⁶⁹⁻¹⁷⁵ and dipole moment measurements.¹⁷⁶ Fewer studies have been made of the association of 3-substituted pyrroles, but it



appears most probable that it is polymeric (26). The association of α - and β -cyanopyrroles, although weaker than that of the corresponding carbonyl compounds, appears to be similar.¹⁷⁷

- ¹⁶⁵ R. A. Jones and A. G. Moritz, *Spectrochim. Acta* **21**, 295 (1965).
¹⁶⁶ R. W. Guy and R. A. Jones, *Australian J. Chem.* **19**, 107 (1966).
^{166a} R. W. Guy and R. A. Jones, *Spectrochim. Acta* **21**, 1011 (1965).
¹⁶⁷ P. Pratesi and V. Berti, *Atti 10th Congr. Intern. Chim., Rome, 1938* Vol. 3, p. 313. Citta Univ., Rome, 1939; *Chem. Abstr.* **33**, 9320 (1939).
^{167a} P. Pratesi and V. Berti, *Boll. Sci. Fac. Chim. Ind. Bologna* **1**, 188 (1940); *Chem. Abstr.* **37**, 639 (1943).
¹⁶⁸ M. T. Sardiña and C. Bonino, *Boll. Sci. Fac. Chim. Ind. Bologna* **12**, 155 (1954); *Chem. Abstr.* **49**, 10709 (1955).
¹⁶⁹ A. M. Buswell, J. R. Downing, and W. H. Rodebush, *J. Am. Chem. Soc.* **62**, 2759 (1940).
¹⁷⁰ G. B. Bonino and P. Chiorboli, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **10**, 104 (1951); *Chem. Abstr.* **46**, 494 (1952).
¹⁷¹ P. Mirone and V. Lorenzelli, *Ann. Chim. (Rome)* **48**, 881 (1958).
¹⁷² P. Mirone and V. Lorenzelli, *Ann. Chim. (Rome)* **49**, 59 (1959).
¹⁷³ L. D. Miroshnichenko, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.* **33**, 2885 (1963); *Chem. Abstr.* **60**, 2451 (1964).
¹⁷⁴ M. K. A. Khan and K. J. Morgan, *J. Chem. Soc.* p. 2579 (1964).
¹⁷⁵ R. Grigg, *J. Chem. Soc.* 5149 (1965).
¹⁷⁶ A. Marinangelli and C. Bonino, *Ann. Chim. (Rome)* **44**, 949 (1954).
¹⁷⁷ L. F. Elsom, M.Sc. Thesis, University of East Anglia (1966).

III. Physicochemical Properties

A. NONSPECTROSCOPIC MEASUREMENTS

1. Basicity and Acidity Measurements

The formation of salts, or adducts, in the reactions between pyrroles and proton acids or Lewis acids has been described by numerous investigators.^{24, 178-197} In many instances it has been shown these products are the salts of the pyrrole dimer and in the case of the unsubstituted pyrrole it is known that a trimer is readily formed in dilute aqueous acid.^{178, 179, 198} Higher polymeric products have also been reported.¹⁹⁹ Relatively few monomeric pyrrole salts have been isolated,^{186, 188} but proof of their existence in solution has been reported.^{189-193, 200-202}

Three alternative sites for protonation of the pyrrole ring are possible (27, 28, and 29). The incorporation of the electron pair on the

¹⁷⁸ M. Dennstedt, *Chem. Ber.* **21**, 3429 (1888); **22**, 1920 (1889); **24**, 2559 (1891).

¹⁷⁹ M. Dennstedt and F. Voigtländer, *Chem. Ber.* **27**, 476 (1894).

¹⁸⁰ G. Ciamician and C. M. Zanetti, *Chem. Ber.* **26**, 1711 (1893).

¹⁸¹ M. Dennstedt and J. Zimmermann, *Chem. Ber.* **19**, 2189 (1886); **20**, 850 (1887); **21**, 1478 (1888).

¹⁸² H. Fischer and G. Stangler, *Ann. Chem.* **459**, 53 (1927).

¹⁸³ H. Fischer, E. Baumann, and H. J. Riedl, *Ann. Chem.* **475**, 205 (1929).

¹⁸⁴ A. Treibs and P. Dieter, *Ann. Chem.* **513**, 65 (1934).

¹⁸⁵ P. Pratesi, *Gazz. Chim. Ital.* **60**, 658 (1935).

¹⁸⁶ J. Stedman and S. F. MacDonald, *Can. J. Chem.* **33**, 468 (1955).

¹⁸⁷ A. Treibs and H. G. Kolm, *Ann. Chem.* **606**, 166 (1957).

¹⁸⁸ E. Bullock, *Can. J. Chem.* **36**, 1686 (1958).

¹⁸⁹ R. J. Abraham, E. Bullock, and S. S. Mitra, *Can. J. Chem.* **37**, 1859 (1959).

¹⁹⁰ E. B. Whipple, Y. Chiang, and R. L. Hinman, *J. Am. Chem. Soc.* **85**, 26 (1963).

¹⁹¹ Y. Chiang and E. B. Whipple, *J. Am. Chem. Soc.* **85**, 2763 (1963).

¹⁹² R. L. Hinman and S. Theodoropoulos, *J. Org. Chem.* **28**, 3052 (1963).

¹⁹³ Y. Chiang, R. L. Hinman, S. Theodoropoulos, and E. B. Whipple, *Tetrahedron* **23**, 745 (1967).

¹⁹⁴ O. Piloty and S. J. Thannhauser, *Ann. Chem.* **390**, 191 (1912).

¹⁹⁵ O. Piloty, K. Wilke, and A. Blömer, *Ann. Chem.* **407**, 1 (1915).

¹⁹⁶ C. F. H. Allen, D. M. Young, and M. R. Gilbert, *J. Org. Chem.* **2**, 235 (1938).

¹⁹⁷ J. H. Atkinson, R. Grigg, and A. W. Johnson, *J. Chem. Soc.* 893 (1964).

¹⁹⁸ H. A. Potts and G. F. Smith, *J. Chem. Soc.* 4018 (1957).

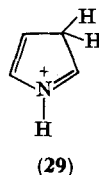
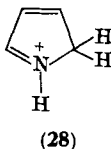
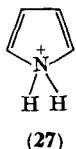
¹⁹⁹ G. F. Smith, *Advan. Heterocyclic Chem.* **2**, 287 (1963).

²⁰⁰ N. F. Hall, *J. Am. Chem. Soc.* **52**, 5115 (1930).

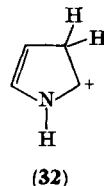
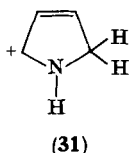
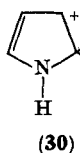
²⁰¹ M. Tamres, S. Searles, E. M. Leighly, and D. W. Mohrman, *J. Am. Chem. Soc.* **76**, 3983 (1954).

²⁰² N. Naqvi and Q. Fernando, *J. Org. Chem.* **25**, 552 (1960).

nitrogen atom into the aromatic sextet suggests that protonation on that atom (**27**) would be unlikely and there is no evidence that this type of protonation occurs in solution. This may not, however, be true of the crystalline salts.¹⁸⁸ The IR spectra of the hydrochlorides of several alkyl pyrroles, measured in the solid phase, may be interpreted in terms of the *N*-protonated form.¹⁸⁸ These salts are not stable in aqueous solution, but are said to dissociate to the free base and then to



redissolve as one of the alternative *C*-protonated forms. These two forms are stabilized as resonance hybrids of the canonical forms **28** with **30** and **31** and **29** with **32**. Molecular orbital calculations,⁷⁹ using the extended Hückel and CNDO II methods, also suggest $\alpha > \beta > N$ as the relative order of basicities of the three positions.



NMR studies have played a considerable part in the elucidation of the sites of protonation of the pyrroles in solution.¹⁸⁹⁻¹⁹³ It is possible to determine the site of protonation both from the changes in the degree of spin-spin coupling of the ring protons¹⁸⁹⁻¹⁹¹ and also from a comparison of the chemical shifts of ring protons of the protonated form with those of the free pyrrole base.¹⁸⁹⁻¹⁹¹ Using this technique, in aqueous sulfuric acid the α -protonated salts have been shown to be the more stable, although the observed rates of deuterium exchange suggest that β -protonation occurs at the faster rate.¹⁹¹ Generally, an alkyl group in the α -position directs protonation to the α' -position, while protonation in the adjacent α -position is observed for β -alkylpyrroles. The simultaneous formation of both α - and β -protonated forms has been observed for α, α' -dialkylpyrroles.¹⁹⁰ For 2,5-dimethyl- and 1,2,5-trimethylpyrrole the α - and β -protonated forms are present

TABLE VII
UV ABSORPTION OF ALKYL AND ARYL PYRROLES AND THEIR CONJUGATE ACIDS

Substituents	Free base ^a		Conjugate acid ^b		C _{H₂SO₄} ^c	Ref.
	λ (nm)	ε	λ (nm)	ε		
—	205	6,700	241 (α)	3,900 ^d	7.6	191–193
1-Methyl	210	5,800	247 (α)	4,100	7.2	192, 193
2-Methyl	208	7,100	233 (α)	4,500	4.3	191–193
3-Methyl	208	5,900	258	4,800	4.8	191, 192
1,2-Dimethyl	210	7,200	240	4,500	5.1	191, 192
2,3-Dimethyl	208	5,600	246	3,800	5.7	191, 192
2,4-Dimethyl	209	5,800	249	5,200	4.0	191, 192
2,5-Dimethyl	209	7,700	237 (α) ^e	4,100	2.5	193
			275 (β)	2,500		
3,4-Dimethyl	205	4,400	217	5,800	4.0	191, 192
1,2,5-Trimethyl	211	8,300	243 (α)	4,850	3.0	193
			280 (β) ^f	2,600		
2,3,4-Trimethyl	208	5,100	262	5,000	6.8	191, 192
2,3,5-Trimethyl	212	6,600	252	5,700	4.0	191, 192
1,2,3,5-Tetramethyl	216	7,500	259	5,600	5.1	191, 192
2,3,4,5-Tetramethyl	216	5,800	265	5,200	2.0	191, 192
1,2,3,4,5-Pentamethyl	216	7,000	269	5,600	5.1	191, 192
1-Phenyl	248	11,300	239	2,400	12.0	193
			244	3,200		
2,5-Dimethyl-1-phenyl	230	5,230	239 (α)	5,700	4.5	193
			270 (β)	28,000		
1-(2',6'-Dimethyl-phenyl)	207 ^h	15,400	207	7,700	12.0	193
	203 ^h	3,500	250	5,440		
			287	840		
2,5-Dimethyl-1-(2',6'-dimethylphenyl)	207	13,100	206	8,550	9.4	193
			252 ^g	8,700		
1- <i>p</i> -Nitrophenyl	225	12,200	213 ^h	7,350	18.0	193
	330	15,500	242	4,310		
			311	14,300		
2,5-Dimethyl-1- <i>p</i> -carboxyphenyl	215	13,100	227 (α)	10,400	6.5	193
	251	7,200	272 (β)	48,200		
1-(2',6'-Dimethyl-4-hydroxyphenyl)	275	930	214	6,700	12.5	193
			250	6,050		
2,5-Dimethyl-1-(4'-hydroxy-2',6'-dimethylphenyl)	272	1,000	215	7,000	9.4	193
	278	930	250 ^g	6,300		

^a Measured as aqueous solutions.

^b Measured in sulfuric acid; (α) denotes band ascribed to α-protonated form, (β) to the β-protonated form.

in a ratio of approximately 2:1, whereas, for 2,5-dimethyl-1-phenylpyrrole the α -protonated conjugate acid is preferred by a factor of 5:1.¹⁹⁰ The introduction of methyl groups into the 2',6'-positions of the phenyl ring of 2,5-dimethyl-1-phenylpyrrole appears to hinder sterically α -protonation and the two conjugate acids are present in approximately equal amounts.¹⁹³ The reduction of 2,5-dimethylpyrrole in hydrochloric acid with zinc to give the Δ^3 - and Δ^1 -pyrrolines in a ratio of 4:1 correlates well with the ease of formation of both the α - and β -conjugate acids and indicates that the initial protonation determines, to a large extent, the structure of the reduction products.¹⁸⁷

The conclusions reached from the NMR results are supported by ultraviolet (UV) absorption data (Table VII). The absorption maxima of the conjugate acids are shifted bathochromically from those of the free pyrrole base and, in general, are of lower intensity. The band in the 235–250 nm region has been assigned to the α -protonated form and the additional band or shoulder near 270 nm indicates the presence of the β -protonated form.¹⁹⁰ The intensities recorded in Table VII have, where necessary, been corrected for the relative concentrations of the α - and β -conjugate acids, and, in several cases, where the intensity of the tail absorption attributable to the α -peak is uncertain, the recorded intensity of the band for the β -conjugate acid can only be approximate. This is true particularly for the 1-phenyl compounds in which the phenyl ring causes a pronounced enhancement of the absorption in the 270-nm region.¹⁹³

The basicities of the pyrroles have been determined spectrophotometrically (Table VIII). It appears that the equilibria for both α - and β -protonation follow the H_R acidity function.¹⁹³ The more reliable results are those obtained from measurements made on dilute solutions of the pyrroles in aqueous acid using this acidity function. Several of the earlier measurements assumed the pyrroles to be H_0 bases and the reported pK_a values tend to be high.^{189–191} For pyrroles which protonate both in the α - and β -positions the relative basicities for the two positions were calculated from the observed

^c Molarity of sulfuric acid in which conjugate acid spectra were measured.

^d $\epsilon = 7900$ has been reported.

^e Earlier work reports 237 nm (2900) and 275 nm (740).

^f Earlier work reports 243 nm (3100) only.

^g Tail absorption ($\bullet = 3100$) at 270 nm suggests the presence of the β -protonated form.

^h Inflection.

TABLE VIII
BASE STRENGTHS OF ALKYL AND ARYL PYRROLES

Substituent	pK _a	Position of protonation	Method of determination ^a	Ref.
—	—3.80	α	A	191
	—4.40	α	B	193
1-Methyl	—2.90	α	A	191
	—3.40	α	B	193
2-Methyl	—0.21	α	A	191
3-Methyl	—1.00	α	A	191
2,4-Dimethyl	2.55	α	A	191
	2.12	α	D	188
	1.9	α	C	189
2,5-Dimethyl	—0.71	α 0.42 ^b	A	190, 191
	—0.80	α	B	193
	—1.07	β	A	190
	—1.20	β	B	193
3,4-Dimethyl	0.66	α	A	191
1,2,5-Trimethyl	—0.20	α 0.56 ^b	B	193
	—0.24	α	A	190, 191
	—0.49	β	A	190
	—0.50	β	B	193
2,3,4-Trimethyl	3.9	α	C	189
3-Ethyl-2,4-dimethyl	3.5	α	C	189
	2.84	α	D	188
2,3,5-Trimethyl	2.00	α	A	191
2,3,4,5-Tetramethyl	3.7	α	C	189
1-Phenyl	—5.8	α	B	193
2,5-Dimethyl-1-phenyl	—2.01	α 0.19 ^b	A	190
	—2.30	α	B	193
	—2.73	β	A	190
	—3.00	β	B	193
1-(2',6'-Dimethylphenyl)	—6.3	α	B	193
2,5-Dimethyl-1-(2',6'- dimethylphenyl)	—3.9	α 1.9 ^b	B	193
	—3.6	β	B	193
2,5-Dimethyl-1- <i>p</i> - carboxyphenyl	—2.9	α 0.16 ^b	B	193
	—3.7	β	B	193
1-(2',6'-Dimethyl-4'- hydroxyphenyl)	—6.0	α	B	193
2,5-Dimethyl-1-(2',6'- dimethyl-4'-hydroxy- phenyl)	—3.3	α 1.3 ^b	B	193
	—3.2	β	B	193

composite pK_a value and the ratio of α - to β -protonation measured by NMR spectroscopy.

Although the OD stretching frequency of methanol-*d*, when measured in the presence of a basic compound, may be correlated with the pK_a of the base such that the results are in good agreement with those obtained by other methods,²⁰¹ the method cannot be used for pyrroles. It is significant that the interaction between methanol and pyrrole can be either through the $-\text{OH}-\pi$ or the $-\text{NH}-\text{O}$ hydrogen bonds and is most certainly not a σ -complex of the type envisaged for the α - or β -conjugate acids. Hence, the pK_a value of 1.7 calculated from the reported 161-cm^{-1} frequency shift of methanol-*d* in pyrrole^{189, 201} bears little relation to the basicity of the ring as measured by UV or NMR spectroscopy. The reported pK_a value of -3.8 for pyrrole,¹⁹¹ measured spectrometrically at 240 nm, when corrected to the H_R scale gives a value of -4.4 ¹⁹³ which is considerably lower than earlier values.²⁰⁰⁻²⁰² In many instances, the earlier workers reported the solutions to be unstable. This suggests that, during the spectral measurement of the conjugate acid, trimerization occurred through reaction between the conjugate acid with the free base as a consequence of the incomplete protonation.¹⁹⁸

Alkylation on either nitrogen or a carbon atom has a profound base-strengthening effect. *N*-Phenyl groups, however, are effectively electron withdrawing and decrease the basicity of the pyrrole ring. Steric hindrance to coplanarity of the two rings reduces their electronic interaction such that the basicity of 2,5-dimethyl-1-(2,6-dimethylphenyl)pyrrole is very close to that of pyrrole¹⁹³ (cf. Sections III, A, 2 and III, B, 3, a). Alkyl groups in the 2,5-positions of the pyrrole ring or the 2,6-positions of the phenyl ring also sterically inhibit solvation of the positively charged pyrrolyl nitrogen atom resulting in a decrease in basicity of *ca.* 0.5 pK unit.

Pyrroles having electron-withdrawing substituents are considerably less basic than alkyl pyrroles. Whereas there appears to be strong UV spectral evidence for the existence of the conjugate acids of

^a A: Spectroscopically using dilute solutions in aqueous sulfuric acid. pK_a values calculated using H_0 . B: Spectroscopically using dilute solutions in aqueous sulfuric acid. pK_a values calculated using H_R . C: Spectroscopically using phosphate-citric acid buffers. D: Spectroscopically using dilute solutions in aqueous hydrochloric acid.

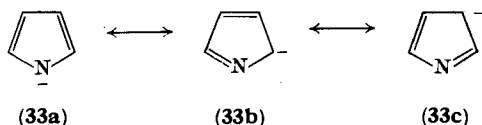
^b The ratio of α - to β -protonation.

acyl¹⁸⁷ and nitro pyrroles,²⁰³ the data for alkoxy carbonyl²⁰⁴ compounds is less conclusive. Stable salts have been isolated for both acyl¹⁸⁷ and nitroso pyrroles,²⁰³ but the available evidence suggests that, unlike the alkyl pyrroles, protonation has occurred not on the ring carbon atoms but on the acyl or nitroso oxygen atoms.²⁰⁵⁻²⁰⁷

Solid chloroplatinate, chloroaurate, cyanoferrate, and cyanoferrite salts and adducts with antimony trichloride and calcium chloride have been reported for alkyl, acyl, and alkoxy carbonyl pyrroles.^{24, 185} The nature of bonding has not been elucidated and it is possible that the compounds are π complexes rather than σ complexes, as may also be the picrates which have been isolated with alkyl pyrroles. The complexes involving the acyl and alkoxy carbonyl pyrroles most probably involve bonding with the substituent rather than the pyrrole ring.

Amino pyrroles, although unstable, form stable picrates.²⁰⁸⁻²¹¹ The structure of these adducts has not been determined and they could either be true salts, with protonation either on the pyrrole ring or the amino group, or, alternatively, charge-transfer π complexes. There is evidence that in trifluoroacetic acid α -aminopyrroles are protonated on the ring carbon atom and most probably in the α' -position.²¹²

Pyrroles having no substituent on nitrogen can readily lose a proton to form the resonance-stabilized pyrrolyl anion (**33a-c**). Pyrrole is a



²⁰³ M. A. T. Rogers, *J. Chem. Soc.* 590 (1943).

²⁰⁴ G. H. Cookson, *J. Chem. Soc.* 2789 (1953).

²⁰⁵ R. W. Guy, Ph.D. Thesis, University of Adelaide (1965).

²⁰⁶ Y. E. Skylar, R. P. Evstigneeva, O. D. Saralidze, and N. A. Preobrazhenskii, *Dokl. Akad. Nauk SSSR* **157**, 367 (1964); *Chem. Abstr.* **61**, 9381 (1964).

²⁰⁷ Y. E. Skylar, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Khim. Geterotsikl. Soedin.*, *Akad. Nauk Latv. SSR* p. 216 (1966); *Chem. Abstr.* **65**, 2199 (1966).

²⁰⁸ H. Fischer, H. Guggemos, and A. Schäfer, *Ann. Chem.* **540**, 30 (1939).

²⁰⁹ H. Fischer and F. Rothweiler, *Chem. Ber.* **56**, 512 (1923).

²¹⁰ H. Fischer and A. Stern, *Ann. Chem.* **446**, 229 (1926).

²¹¹ F. Endermann and H. Fischer, *Ann. Chem.* **538**, 172 (1939).

²¹² C. T. Wie, S. Sunder, and C. De Witt, *Tetrahedron Letters* 4605 (1968).

somewhat weaker acid than methanol—a pK value of 17.51 ± 0.5 has been determined spectroscopically,²¹³ although an earlier evaluation gave 16.5.²¹⁴

Alkali metal salts of pyrrole are formed from the reaction of pyrrole with metals in liquid ammonia,²¹⁵ and also with potassium in petroleum ether²¹⁶ or toluene.²¹⁷ Pyrrole will also react with fused potassium hydroxide. The sodium and lithium salts are readily formed using sodium hydride and butyl- or phenyllithium.^{215, 218, 219} Calcium,²²⁰ silver,²²⁰ thallium,²²¹ chromium,²²² manganese^{223, 223a} and iron^{223a-d} derivatives have also been described. Alkyl pyrroles have been shown to form stable compounds with organic bases.²²⁴ Alkyl Grignard reagents react with pyrroles²²⁵ with liberation of the alkane to give the pyrrolyl Grignard compound. The pyrrolyl metal compounds formed by any of these methods can conceivably react with electrophiles to give either the 1-, 2-, or 3-substituted products. There is, however, a distinct difference in the ratio of the products obtained from the reactions of alkyl halides with the alkali metal salts and with the pyrrolyl Grignard compounds.²²⁶ NMR data indicate that both

²¹³ G. Yagil, *Tetrahedron* **23**, 2855 (1967).

²¹⁴ W. K. McEwen, *J. Am. Chem. Soc.* **58**, 1124 (1936).

²¹⁵ A. Treibs and A. Dietl, *Ann. Chem.* **619**, 80 (1958).

²¹⁶ See, for example, J. E. Reynolds, *J. Chem. Soc.* **95**, 505 (1909).

²¹⁷ See, for example, J. L. Rainey and H. Adkins, *J. Am. Chem. Soc.* **61**, 1104 (1939).

²¹⁸ E. R. Alexander, A. B. Herrick, and T. M. Roder, *J. Am. Chem. Soc.* **72**, 2760 (1950).

²¹⁹ D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.* **20**, 225 (1955).

²²⁰ E. C. Franklin, *J. Phys. Chem.* **24**, 81 (1920).

²²¹ A. McKillop and E. C. Taylor, private communication (1968).

²²² D. Tille, *Z. Naturforsch.* **21b**, 1239 (1966).

²²³ K. K. Joshi and P. L. Pauson, *Proc. Chem. Soc.* 326 (1962).

^{223a} K. K. Joshi, P. L. Pauson, A. R. Qazi, and W. H. Stubbs, *J. Organometal. Chem.* **1**, 471 (1964).

^{223b} R. B. King and M. B. Bisnette, *Inorganic Chem.* **3**, 796 (1964).

^{223c} F. Seel and V. Sperber, *J. Organometal. Chem.* **14**, 405 (1968).

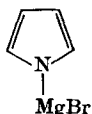
^{223d} K. Bauer, H. Falk, and K. Schlögl, *Angew. Chem. Internat. Edit.* **8**, 135 (1969).

²²⁴ M. Dezelic and B. Belia, *Bull. Soc. Chim. Roy. Yugoslav.* **9**, 151 (1938); *Chem. Abstr.* **34**, 7289 (1940).

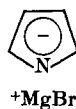
²²⁵ B. Oddo, *Gazz. Chim. Ital.* **39**, 649 (1909).

²²⁶ See, for example, P. S. Skell and G. P. Bean, *J. Am. Chem. Soc.* **84**, 4655 and 4660 (1962); C. E. Griffin and R. Obrycki, *J. Org. Chem.* **29**, 3090 (1964); C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos, and C. A. VanderWerf, *J. Am. Chem. Soc.* **84**, 43 (1962), and references cited therein.

types of pyrrolyl metal compounds have a similar structure.^{227, 228} The Grignard compound may therefore be formulated either as a covalent *N*-substituted pyrrole (34) or as the ionic species (35), but not as the C-Mg compound which has previously been postulated. It is rapidly becoming apparent that the size of the cation, its degree of association with the pyrrolyl anion, and solvation effects, as well as the size of the attacking electrophile, all contribute to the ratio of the alkylation products. The pyrrolyl manganese and iron derivatives have been shown by spectroscopic measurements^{223-223c} to be π -bonded complexes analogous to ferrocene.



(34)



(35)

1-Substituted pyrroles do not react with Grignard reagents or alkali metals, but 1-methyl and 1-phenylpyrrole have been reported to react with *n*-butyllithium to give the α -lithio derivative.²¹⁸

As is to be expected, the acidity of the pyrrolyl NH is increased by electron-withdrawing substituents. Table IX records the pK_a values (as acids) of several nitro pyrroles²²⁹ and pyrrole carboxylic esters²³⁰ that have been determined. The relative acid strengths are also reflected in the NH stretching frequencies of the monomeric pyrroles.²³¹ Substituents that lower the NH stretching frequency to the greatest extent also produce a correspondingly large increase in the acidity (Table XVI, Section III, B, 1) and, in general, a greater change is produced by substituents in the α -position than in the β -position. Nitro and nitrosopyrroles are particularly acidic and readily dissolve in dilute aqueous alkali,^{1, 229, 232-236} as do several other

²²⁷ M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, *J. Am. Chem. Soc.* **85**, 2859 (1963).

²²⁸ A. J. Castro, J. F. Deck, N. C. Ling, J. P. Marsh, and G. E. Means, *J. Org. Chem.* **30**, 344 (1965).

²²⁹ S. S. Novikov, V. M. Belikov, Y. P. Egorov, E. N. Safanova, and L. V. Semenov, *Bull. Acad. Sci. USSR* 1386 (1959); *Chem. Abstr.* **53**, 21149 (1959).

²³⁰ H. Fischer and P. Ernst, *Ann. Chem.* **447**, 139 (1926).

²³¹ M. Scrocco and R. Nicolaus, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **21**, 103 (1956); *Chem. Abstr.* **51**, 4145 (1957).

²³² G. Ciamician and P. Silber, *Chem. Ber.* **18**, 1456 (1885).

TABLE IX
NH ACID IONIZATION CONSTANTS OF PYRROLE AND DERIVATIVES

Substituents				pK _a	Ref.
2	3	4	5		
H	H	H	H	17.51 ± 0.05	213
H	CO ₂ Et	Me	CO ₂ Et	13.1	230
Me	CO ₂ Et	Me	CO ₂ Et	13.4	230
Br	CO ₂ Et	Me	CO ₂ Et	10.5	230
Cl	CO ₂ Et	Me	CO ₂ Et	10.2	230
CO ₂ Et	H	Br	Br	ca. 10.0	237
CO ₂ Et	Br	Br	Br	ca. 10.0	237
CO ₂ Et	Cl	Cl	Cl	ca. 9.0	237
NO ₂	H	H	H	10.60	229
CHO	H	NO ₂	H	9.30	237a
CHO	H	H	NO ₂	6.68	237a
NO ₂	H	NO ₂	H	6.15	229
NO ₂	H	H	NO ₂	3.60	229

pyrroles polysubstituted with electron-withdrawing substituents. The ionization constants of several polyhalogenated pyrroles and cyano pyrroles have been determined by potentiometric titration.^{230,237}

Acid dissociation constants have also been measured for several pyrrole carboxylic acids²³⁸⁻²⁴³ (Table X) and attempts have been made, by taking the reaction constant ρ for ionization as unity, to extrapolate the σ values obtained from the ionization constants of

²³³ H. J. Anderson, *Can. J. Chem.* **37**, 2053 (1959).

²³⁴ T. Ajello, *Gazz. Chim. Ital.* **69**, 315 (1939).

²³⁵ I. J. Rinkes, *Rec. Trav. Chim.* **53**, 1167 (1934); **56**, 1142 (1937).

²³⁶ H. Fischer and W. Zerweck, *Chem. Ber.* **55**, 1949 (1922).

²³⁷ P. Hodge and R. W. Rickards, *J. Chem. Soc.* 459 (1965).

^{237a} P. Fournari, M. Person, G. Watelle-Marian, and M. Delepine, *Compt. Rend.* **253**, 1059 (1961).

²³⁸ M. Scrocco and R. Nicolaus, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **22**, 311 (1957); *Chem. Abstr.* **52**, 50 (1958).

²³⁹ M. K. A. Khan and K. J. Morgan, *Tetrahedron* **21**, 2197 (1965).

²⁴⁰ A. H. Jackson, G. W. Kenner, and D. Warburton, *J. Chem. Soc.* 1328 (1965).

²⁴¹ T. A. Molent'eva, L. V. Kazanskaya, and V. M. Berezovskii, *Dokl. Akad. Nauk SSSR* **175**, 354 (1967); *Chem. Abstr.* **67**, 120484 (1967).

²⁴² P. O. Lumme, *Suomen Kemistilehti* **B33**, 87 (1960); *Chem. Abstr.* **55**, 5104 (1961).

²⁴³ H. Rapoport and C. D. Wilson, *J. Org. Chem.* **26**, 1102 (1961).

TABLE X
IONIZATION CONSTANTS OF PYRROLE CARBOXYLIC ACIDS

Substituents on 2-carboxylic acids			pK _a	Temperature (°C)	Solvent	Ref.
3	4	5				
H	H	H	4.39 ± 0.01	20	H ₂ O	239
			4.40	—	—	238
			4.45 ^a	30	H ₂ O	242
H	Me	H	4.60	—	—	238
H	H	Me	5.00	—	—	238
Me	H	H	5.10	—	—	238
Me	H	Me	7.01	20	50% aq. EtOH	241
			7.93	25	MCS ^b	240
Me	Me	Me	7.30	20	50% aq. EtOH	241
Me	Et	Me	7.36	20	50% aq. EtOH	241
Et	Me	Me	8.24	25	MCS	240
Me	P _{Me}	Me	7.92	25	MCS	240
Me	CO ₂ Et	Me	6.40	20	50% aq. EtOH	241
			7.11	25	MCS	240
Me	COMe	Me	6.17	20	50% aq. EtOH	241
			6.98	25	MCS	240
Me	NO ₂	Me	5.61	20	50% aq. EtOH	241
Me	Et	CONMe ₂	7.03	25	MCS	240
Me	Et	CO ₂ Et	6.40	25	MCS	240
Me	Et	CO ₂ CH ₂ φ	6.40	25	MCS	240
P _{Me}	Me	CO ₂ CH ₂ φ	6.19	25	MCS	240
Me	Et	CN	6.12	20	50% aq. EtOH	241
CO ₂ Et	Me	CO ₂ CH ₂ φ	5.66	25	MCS	240

substituted benzoic acids to the pyrrole-2- and pyrrole-3-carboxylic acids.²³⁹ In this way the σ values of -0.15 and -0.75 have been ascribed to the 2- and 3-substituted pyrrole rings.²³⁹ These results indicate that both positions have a higher electron density than is found in benzene, and although σ values should reflect the relative electron distributions in the ground state, contrary to the observed chemical reactivity of the two positions, it appears that the higher electron density is at the 3-position. In direct contrast to these results, a correlation of the carbonyl stretching frequency of the corresponding esters with the σ^+ constant gives values of -2.0 and -1.5 for the 2- and 3-substituted pyrrole rings, respectively.²³⁹ These anomalous

TABLE X—*continued*
IONIZATION CONSTANTS OF PYRROLE CARBOXYLIC ACIDS

Substituents on 3-carboxylic acids			pK _a	Temperature (°C)	Solvent	Ref.
2	4	5				
H	H	H	4.95	—	—	238
			5.00 ± 0.01	20	H ₂ O	239
			5.07	—	—	243
H	H	Me	5.35	—	—	238
H	Me	H	5.65	—	—	238
Me	H	H	5.80	—	—	238
			5.75	—	—	243
Me	Me	H	7.83	20	50% aq. EtOH	241
Me	Me	CO ₂ Et	7.30	20	50% aq. EtOH	241
Me	Me	COMe	6.98	20	50% aq. EtOH	241
Me	Me	NO ₂	6.58	20	50% aq. EtOH	241

^a Thermodynamic pK_a. Correction of Morgan's value gives pK_a' at 20°C of 4.43.

^b Methyl Cellosolve-water (78.5:31.5 v/v).

P_{me} = CH₂CH₂CO₂CH₃

pairs of results may be the result of an abnormally high ionization constant for the 2-carboxylic acid compared with the 3-carboxylic acid, resulting from the increased stability of the anion arising from intramolecular hydrogen bonding.

The pK_a values for a series of 4-substituted 3,5-dimethylpyrrole-2-carboxylic acids and 5-substituted 2,4-dimethylpyrrole-3-carboxylic acids have been correlated with the substituent σ constants.²⁴¹ The σ_{meta} constants were used for the 3-carboxylic acids and the σ_{para} constants for the 2-carboxylic acids. In assuming the use of σ_{para} constants for the 5-substituents of the 2-carboxylic acids the NH group was considered to be equivalent to the C=C bond of the benzene ring and any electronic effect of the pyrrole ring upon the ionization constant, as described by the σ values by Morgan and Khan²³⁹ has been neglected. The calculated ρ value of 1.43 was rationalized purely in terms of a better transmission of the substituent effects by the pyrrole ring than by the benzene ring. From the results for the 3-carboxylic acids, it is apparent that the steric and electronic effects of the methyl groups are negligible, but with only the limited amount of experimental data, no ρ value was calculated.

2. Dipole Moments

It should be noted that methods of measurement and calculation of dipole moments vary. The values given in this section are as recorded by the original authors. No attempts have been made to correct their data. Most determinations after 1942 have been made using the Halverstadt-Kumler procedure.²⁴⁴ Molecular orbital calculations^{18, 27, 37, 53, 56, 58-60, 63, 66-68, 70, 71, 73, 75, 76, 100, 245-251} (see Section II, A)

TABLE XI
DIPOLE MOMENT OF PYRROLE

Dipole moment (D)	State or solvent	Temperature (°C)	Ref.
1.84 ± 0.08	Gas	15-200	254
1.84	Gas	—	117a
1.54	Liquid	25	255
1.55 - 1.65	Liquid	20-85	110
1.58	Liquid	—	117a
1.74	Benzene	20	47
1.80 ± 0.01	Benzene	25	252
1.80 ± 0.07	Benzene	25	254
1.82 ± 0.01	Benzene	20	256
1.83	Benzene	—	257
1.83	Benzene	20	258
1.83 ± 0.02	Benzene	25	117a
2.2	Benzene	20	259
1.75	Cyclohexane	—	257
1.75 ± 0.02	Cyclohexane	25	117a
1.76	CCl ₄	—	257
1.76 ± 0.02	CCl ₄	25	117a
1.78	CCl ₄	25	260
1.97	Dioxane	20	47
2.14 ± 0.01	Dioxane	—	117
2.15	Dioxane	—	257
2.15 ± 0.02	Dioxane	25	117a

²⁴⁴ I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.* **64**, 2988 (1942).

²⁴⁵ J. P. Dahl and A. E. Hansen, *Theoret. Chim. Acta* **1**, 199 (1963).

²⁴⁶ L. B. Kier, *Tetrahedron Letters* 3273 (1965).

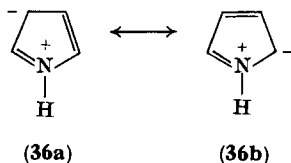
²⁴⁷ B. Zurawski, *Bull. Acad. Polon. Sci., Ser. Sci. Math., Astron. Phys.* **14**, 401 (1966); *Chem. Abstr.* **66**, 69126 (1967).

²⁴⁸ D. W. Davies and W. C. Mackrodt, *Chem. Commun.* 1226 (1967).

²⁴⁹ N. S. Hush and Y. R. Yandle, *Chem. Phys. Letters* **1**, 493 (1967).

²⁵⁰ W. Adam and A. Grimson, *Theoret. Chim. Acta* **7**, 342 (1967).

suggest that pyrrole should have a significant π moment and that the overall dipole moment should lie along the symmetry axis such that the positive pole is toward the nitrogen atom and the negative pole toward the ring. As there are no lone pairs of electrons in pyrrole, the atomic polarization, resulting from the mixing of s and p orbitals on each atom, would be expected to be small. Calculations²⁵² using the generally accepted σ moments for the H-C, H-N, and C-N bonds and assuming a regular pentagonal structure of side length ~ 1.4 Å give a value of ~ 0.4 Debye for this term. Values of between 1.0 and 1.6 Debye have been calculated^{27, 76, 251} for the π moment from the reported charge distribution on the ring. This gives a total calculated dipole moment in the range 1.5–2.0 Debye, which is in good agreement with experimentally determined values. (Table XI). Higher values for the π moment have also been suggested,^{53, 66–68a, 100, 250} which require that the σ moment be negligibly small such that it may be neglected, and, in several calculations, the direction of the σ moment has been postulated to be opposite to that calculated using the generally accepted bond moments. That the overall dipole is positive in the direction suggested, has been confirmed by a study of alkylated derivatives.²⁵² This reaffirms the importance of the contribution of the formally charged structures (36a and 36b) to the resonance hybrid and confirms the incorporation of the electron pair on nitrogen into the aromatic sextet (cf. the dipole direction for amines²⁵³).



²⁵¹ H. Hamano and H. F. Hametka, *Tetrahedron* **18**, 985 (1962).

²⁵² H. Kofod, L. E. Sutton, and J. Jackson, *J. Chem. Soc.* 1467 (1952).

²⁵³ L. E. Sutton in "Determination of Organic Structures by Physical Methods" (E. A. Braude and F. C. Nachod, eds.), Vol. 1, Chapter 9. Academic Press, New York, 1955.

²⁵⁴ A. D. Buckingham, B. Harris, and R. J. W. LeFèvre, *J. Chem. Soc.* 1626 (1953).

²⁵⁵ L. Jannelli and P. G. Orsini, *Gazz. Chim. Ital.* **89**, 1467 (1959).

²⁵⁶ H. de Vries Robles, *Rec. Trav. Chim.* **58**, 111 (1939).

²⁵⁷ H. Lumbruso and G. Pappalardo, *Bull. Soc. Chim. France* 1131 (1961).

²⁵⁸ E. G. Cowley and J. R. Partington, *J. Chem. Soc.* 1259 (1933).

²⁵⁹ W. Hückel, J. Datow, and E. Simmessbach, *Z. Physik. Chem.* **A186**, 166 (1940).

Prior to the microwave determination of the structure of pyrrole,²⁰ which showed unequivocally that pyrrole has C_{2v} symmetry with the NH bond in the plane of the ring, attempts were made using dipole moment measurements to clarify the contradictory conclusions deduced from the then available infrared data. Although the results from the dipole moment measurements tended to show that as far as pyrrole and 1-methylpyrrole were concerned the NH and NMe bonds were roughly coplanar with the ring, the data, in general, failed to be conclusive. An anomalously large enhancement of the moment for pyrrole upon 1-methylation still requires an adequate explanation, and somewhat conflicting results were obtained from the 1-arylpyrroles (Table XII).

TABLE XII
DIPOLE MOMENTS OF 1-ARYLPYRROLES^a

1-Substituent	Dipole moment (<i>D</i>)
1-Arylpyrroles	
Phenyl	1.32 ± 0.04
<i>p</i> -Tolyl	1.79 ± 0.04
<i>p</i> -Chlorophenyl	ca. 0.3
2,5-Dimethyl-1-arylpyrroles	
Phenyl	2.00 ± 0.04
<i>p</i> -Tolyl	2.34 ± 0.02
2,5-Xylyl	2.07 ± 0.02
Mesityl	2.06 ± 0.04
<i>p</i> -Chlorophenyl	0.50 ± 0.04
<i>p</i> -Bromophenyl	0.54 ± 0.04
<i>p</i> -Nitrophenyl	2.48 ± 0.02
Compound 38	0.77 ± 0.03

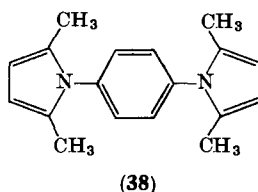
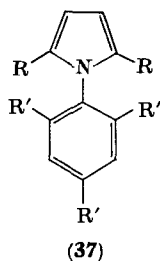
^a At 25° in benzene.

The observed moment for 1-phenylpyrrole indicates a certain degree of interannular conjugation (cf. NMR data,²⁶¹ Section III, B, 3, a) which opposes the π moment of the pyrrole ring.²⁵² Further evidence is provided by a comparison of the moment of 1-

²⁶⁰ C. G. LeFèvre, R. J. W. LeFèvre, B. Purnachandra Rao, and M. R. Smith, *J. Chem. Soc.* 1188 (1959).

²⁶¹ R. A. Jones, T. M. Spotswood, and P. Cheuychit, *Tetrahedron* **23**, 4469 (1967).

phenylpyrrole with the data from compounds in which methyl groups in positions *ortho* to the interannular bond inhibit, by steric interference, the interannular conjugation. The very close agreement obtained between calculated and observed moments for 1-*p*-substituted aryl pyrroles confirms the presence of interannular conjugation and also provides evidence for the collinearity of the axes of the two rings.²⁵² The observed dipole moment for 2,5-dimethyl-1-mesitylpyrrole (**37**, R=R'=Me) is in reasonably good agreement with the calculated value assuming virtually no interannular conjugation. However, there is rather inconclusive evidence for a departure from collinearity of about 6°–7° for 1-phenyl-2,5-dimethylpyrrole (**37**, R=Me, R'=H).²⁵² This appears to be unlikely in view of



the recent NMR measurements²⁶¹ for these compounds which suggest that the major interaction between the π systems is inductive. Thus, although the two rings are certainly not coplanar, some interaction between the two π systems is possible. In the interpretation of the dipole moment data inductive interactions were not considered. An extremely unexpected result was observed for *p*-bis(2,5-dimethyl-1-pyrrolyl)benzene (**38**). This compound should be nonpolar if the axes are collinear. The observed moment²⁵² of 0.77 Debye can be reconciled only with the pyrrole-phenyl axes being out of line by about 32° in a *syn* configuration. Such a structure is, however, highly improbable. The alternative explanation that the moment arises from atomic polarization is possible, but the size of the moment suggests that this is not entirely the answer. The unsatisfactory situation of this particular problem warrants further investigation.

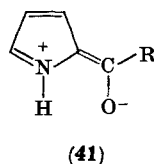
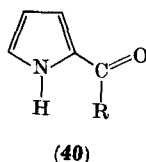
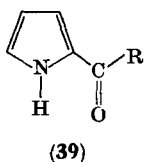
The dipole moments of several different classes of substituted pyrroles have been measured and are recorded in Table XIII.

The observed dipole moments for 2-formyl- and 2-acetylpyrrole have been correlated⁴⁷ with the conformer (**39**, R=H or Me); the

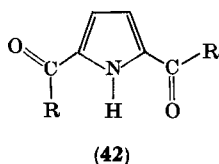
TABLE XIII
DIPOLE MOMENTS OF SUBSTITUTED PYRROLES

Substituent	Dipole moment (D)	State or solvent	Temperature (°C)	Ref.
1-Methyl	2.11	Gas	—	117a
	1.73	Liquid	25	117a
	1.92 ± 0.02	Benzene	25	251
	1.98 ± 0.02	Benzene	25	117a
	1.96 ± 0.02	Cyclohexane	25	117a
	1.92 ± 0.02	CCl ₄	25	117a
	2.03 ± 0.02	Dioxane	25	117a
2-Methyl	1.89	Benzene	25	267
2,4-Dimethyl	1.75	Benzene	25	267
2,5-Dimethyl	2.03	Benzene	25	267
	2.08 ± 0.03	Benzene	25	252
1,2,5-Trimethyl	2.07 ± 0.01	Benzene	25	267
1-Acetyl	2.44	Benzene	20	268
	2.58	Benzene	25	267
	2.52	Dioxane	20	268
2-Acetyl	1.52	Benzene	20	47
	1.79	Dioxane	20	47
2-Formyl	1.88	Benzene	20	47
	2.42	Dioxane	20	47
2,5-Diacetyl	3.93	Dioxane	20	47
2-Methoxycarbonyl	1.70	Benzene	25	269
3-Methoxycarbonyl	3.65	Benzene	25	269
3,4-Diethoxycarbonyl	4.08	Benzene	25	269
3-Ethoxycarbonyl-2-methyl	3.43	Benzene	25	269
3-Ethoxycarbonyl-5-methyl	3.84	Benzene	25	269
3,4-Diethoxycarbonyl-5-methyl	4.31	Benzene	25	269
2,3-Diethoxycarbonyl-5-methyl	2.84	Benzene	25	269
1-Methyl-2-nitro	4.67	Benzene	25	270
1-Methyl-3-nitro	6.15	Benzene	25	270
3,4-Diiodo-2,5-dimethyl	4.00 ± 0.01	Benzene	25	252
2,3,4,5-Tetraiodo	2.52 ± 0.04	Benzene	25	252

moment calculated for the alternative conformer (40) being considerably larger than the observed values. These results have been supported by IR¹⁶⁶ and NMR²⁶²⁻²⁶⁶ measurements. However, although the importance of the zwitterionic canonical form (41) was realized, no attempts were made to calculate the interaction moment.



By similar calculations the structure of 2,5-diacetylpyrrole has been shown to be 42.⁴⁷ Further evidence for this conformation was provided by spectroscopic measurements.^{166, 271} Conclusions regarding the



conformations of pyrrole carboxylic esters²⁶⁹ also ignore interaction moments and are therefore somewhat suspect in that they fail to consider the importance of the zwitterionic canonical structures. Recent investigations,²⁷⁰ however, have attempted to determine the size of the interaction moment. Its value will depend largely on the electron-withdrawing ability of the substituent and also on its position. Although precise values are not available, interaction moments of

²⁶² G. J. Karabatsos and F. M. Vane, *J. Am. Chem. Soc.* **85**, 3886 (1963).

²⁶³ R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **39**, 905 (1961).

²⁶⁴ S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi* **18**, 133 (1962).

²⁶⁵ M. K. A. Khan, K. J. Morgan, and D. P. Mooney, *Tetrahedron* **22**, 2095 (1966).

²⁶⁶ R. A. Jones and P. H. Wright, *Tetrahedron Letters* 5495 (1968).

²⁶⁷ E. N. Gur'yanova, L. A. Yanovskaya, and A. P. Terent'ev, *Zh. Fiz. Khim.* **25**, 897 (1951); *Chem. Abstr.* **46**, 2360 (1952).

²⁶⁸ A. Marinangelli, *Ann. Chim. (Rome)* **44**, 880 (1954).

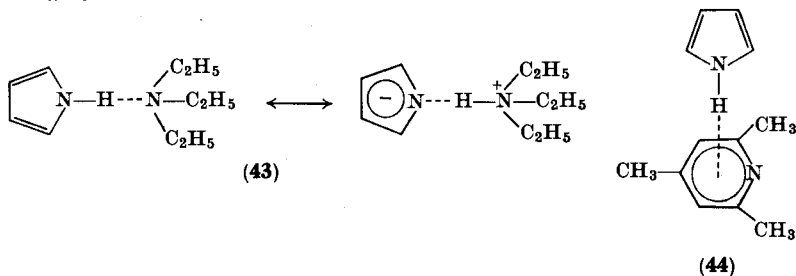
²⁶⁹ L. Janelli and R. A. Nicolaus, *Gazz. Chim. Ital.* **89**, 1457 (1959).

²⁷⁰ H. Lumbroso and C. Carpanelli, *Bull. Soc. Chim. France* 3198 (1964).

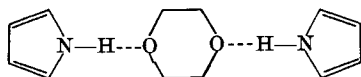
²⁷¹ V. Lorenzelli and F. Cappellina, *Ann. Chim. (Rome)* **48**, 866 (1958).

1.1 and 1.15 Debye have been calculated for 1-methyl-2- and 1-methyl-3-nitropyrroles, respectively, and correspond to *ca.* 0.4 $D/\text{\AA}$.²⁶⁹

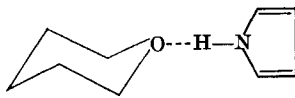
The effect of the autoassociation of pyrrole and its association with solvents and other solutes capable of forming hydrogen bonds on the dipole moment of pyrrole has been studied by several investigators^{47, 110, 111, 117, 117a-c, 255, 257, 259, 272} and the equilibrium constants for the self-association of pyrrole in various solvents have been reported.^{117, 117a-c} The decrease in the dipole moment in changing from the gaseous to the liquid phase is compatible with the formation of the cyclic dimer (cf. NMR data¹¹⁹). The possibility of the open $\text{NH}-\pi$ dimer, however, is not entirely eliminated. The high dipole moments observed for pyrrole when measured in the presence of azines in a nonhydrogen-bonding solvent have been rationalized in terms of 1:1 hydrogen-bonded complexes in which the polar character of the pyrrole ring is enhanced. It has been suggested that the preferred configuration of the complexes formed between pyrrole and triethylamine and between pyrrole and pyridines not having α -substituents is linear (e.g., **43**; cf. Happe¹¹⁹), whereas for the complexes between pyrrole and propionitrile and between pyrrole and 2,4,6-collidine the configuration is orthogonal (**44**). This latter conclusion is particularly surprising in view of the IR studies which suggest the presence of linear hydrogen-bonded complexes (see Section II, B, 2). The formation of only 1:1 complexes between 1,4-dioxane or tetrahydropyran and pyrrole has been confirmed by dipole moment studies,^{117c, 163} and there appears to be little evidence for the 1:2 complex between pyrrole and 1,4-dioxane (**45**). The value of $3.15 \pm 0.1 D$ for the moment of the pyrrole-tetrahydropyran complex has been interpreted^{117c, 163} as the preferential formation of the equatorial complex (**46**) which one would have expected to be the more stable system from steric considerations.



²⁷² S. W. Tucker and S. Walker, *Trans. Faraday Soc.* **62**, 2690 (1966).



(45)



(46)

The dipole moments of bis(2-pyrrolylmethyleneimine)copper(II) complexes have been measured and the results correlated with square planar and tetrahedral configurations.²⁷³

3. Polarographic Properties

A considerable mass of data has been accumulated on the redox potential of pyrrole and its derivatives. A selection of the more reliable data has been tabulated in detail.²⁷⁴ For the most part the data have been used for qualitative structural analysis and until recently^{275, 276} little quantitative significance has been put upon the results. Pyrrole^{277, 278} and its 1-substituted derivatives²⁷⁷⁻²⁸⁰ are not reduced polarographically at a mercury electrode over a wide pH range, and neither are C-alkyl derivatives^{277, 278, 280} or pyrrolyl carboxylic esters,^{277, 278, 281} although the ester groups do aid the reduction of other groups by their electron-withdrawing effect on the ring. Hence, the majority of research has been concentrated on the readily reduced acyl,^{282, 282a-c} formyl,^{277, 281, 282b, 283-290} and nitro^{237a, 291-296}

²⁷³ V. I. Minkin, O. A. Osipo, and D. S. Verkhovodova, *Zh. Neorgan. Khim.* **11**, 2829 (1966); *Chem. Abstr.* **66**, 71989 (1967).

²⁷⁴ J. Volke, *Phys. Methods Heterocyclic Chem.* **1**, 217 (1963).

²⁷⁵ P. Zuman, "Substituent Effects in Organic Polarography." Plenum Press, New York, 1967.

²⁷⁶ P. Zuman, *Collection Czech. Chem. Commun.* **27**, 630 (1962).

²⁷⁷ M. Dezelic, *Rad. Hrvat. Akad.* **271**, 21 (1941); *Chem. Abstr.* **42**, 5899 (1948).

²⁷⁸ G. Scaramelli, *Boll. Sci. Fac. Chim. Ind. Bologna*, **3**, 205 (1942); *Chem. Abstr.* **38**, 6281 (1944).

²⁷⁹ L. Palasciano, *Boll. Sci. Fac. Chim. Ind. Bologna* **2**, 83 (1941); *Chem. Abstr.* **37**, 2642 (1943).

²⁸⁰ G. B. Bonino, *Pontif. Acad. Sci., Acta* **9**, 65 (1945); *Chem. Abstr.* **45**, 7445 (1951).

²⁸¹ G. Scaramelli, *Atti Accad. Ital., Rend. Classe Sci. Fis., Mat. Nat.* **1**, 575 (1940); *Chem. Abstr.* **37**, 1423 (1943).

²⁸² G. Scaramelli, *Boll. Sci. Fac. Chim. Ind. Bologna* **1**, 49 (1940); *Chem. Abstr.* **34**, 2373 (1940).

^{282a} G. Scaramelli, *Boll. Sci. Fac. Chim. Ind. Bologna* **2**, 99 (1941); *Chem. Abstr.* **37**, 4390 (1943).

^{282b} G. Scaramelli, *Chem. Ber.* **75**, 1948 (1942).

derivatives. The half-wave potentials of these compounds depend upon the position of the reducible substituent, the α -compounds being more readily reduced than the β -compounds. Thus, the $E_{1/2}$ values for 2-formyl- and 2-acetylpyrroles lie in the range -1.5 to -1.8 volts; under the same conditions, the 3-substituted compounds are not reduced.^{282, 285a} In many cases it has not been possible to measure the half-wave potential for the 3-acyl derivatives, but values of -2.00 and -2.16 volts have been reported for 2-ethoxycarbonyl-3,5-dimethyl-4-formylpyrrole and 3-formyl-2,4-dimethylpyrrole, respectively.^{285a} Other 3-acyl derivatives have been shown to resist reduction at potentials of -2.40 volts,^{285a} although it does appear that these compounds undergo polarographic reduction in an acidic medium.^{285a} Although there are many conflicting values for the half-wave potential of 2-formylpyrrole, there has been sufficient evidence to confirm the keto structure in preference to the alternative hydroxymethylene form.^{286, 287} The electrode process is pH dependent. 2-Formylpyrrole²⁸⁸ is least readily reduced at pH 7, and similarly for 1-methyl-2-formylpyrrole²⁸⁸ the $E_{1/2}$ values vary steadily from -1.594 volts in acidic media to a maximum negative potential of -1.732 volts at pH 8 and remains constant through to a strongly alkaline solution.^{285b, 287} It has been suggested²⁹⁰ that in strongly

^{282c} G. Scaramelli, *Atti Accad. Ital., Rend. Classe Sci. Fis., Mat. Nat.* **1**, 471 (1940); *Chem. Abstr.* **37**, 375 (1943).

²⁸³ G. Scaramelli, *Boll. Sci. Fac. Chim. Ind. Bologna* **1**, 239 (1940); *Chem. Abstr.* **37**, 5058 (1943).

²⁸⁴ F. Cappellina and A. Drusiani, *Gazz. Chim. Ital.* **84**, 939 (1954).

²⁸⁵ F. Cappellina and V. Lorenzelli, *Ann. Chim. (Rome)* **48**, 893 (1958).

^{285a} F. Cappellina and V. Lorenzelli, *Ann. Chim. (Rome)* **48**, 902 (1958).

^{285b} F. Cappellina and V. Lorenzelli, *Atti Mem. Accad. Sci. Ist. Bologna, Classe Sci. Fis., Sez. Sci. Nat.* [10] **11**, 1 (1958); *Chem. Abstr.* **53**, 7826 (1959).

²⁸⁶ G. B. Bonino and G. Scaramelli, *Ric. Sci.* **6**, 111 (1935).

²⁸⁷ F. Cappellina, *Ann. Chim. (Rome)* **48**, 535 (1958).

²⁸⁸ F. Cappellina and A. Drusiani, *Ric. Sci.* **30** 297 (1960).

²⁸⁹ F. Cappellina and L. Pederzini, *Collection Czech. Chem. Commun.* **25**, 3344 (1960).

²⁹⁰ E. Laviron, *Compt. Rend. Congr. Soc. Savantes Paris Dep., Sect. Sci.* **84**, 201 (1960); *Chem. Abstr.* **55**, 24747 (1961).

²⁹¹ J. Tirouflet and E. Laviron, *Ric. Sci. Suppl.* **4**, 189 (1959).

²⁹² M. Person and J. Tirouflet, *Compt. Rend.* **251**, 2532 (1960).

²⁹³ M. Person, *Compt. Rend.* **255**, 301 (1962).

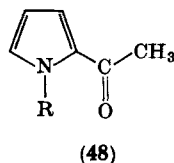
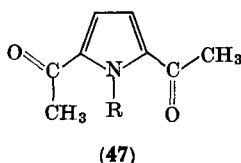
²⁹⁴ P. Fournari, *Bull. Soc. Chim. France* 488 (1963).

²⁹⁵ P. Fournari and J. Tirouflet, *Bull. Soc. Chim. France* 479 (1963).

²⁹⁶ P. Fournari and J. Tirouflet, *Bull. Soc. Chim. France* 1651 (1963).

acidic solutions the reaction is a six-electron reduction to give the saturated alcohol, whereas in neutral and alkaline media a two-electron reduction to the carbinol occurs. There is also evidence for two distinct electrode processes in dimethyl formamide and in water.²⁸⁹ Polarographic data for the aldoximes,^{290, 297} hydrazones,²⁹⁸ semicarbazones,²⁹⁸ and Schiff's bases²⁹⁹ have also been reported.

The observation of two distinctly different $E_{1/2}$ values^{282, 282a} for 2,5-diacetylpyrrole was originally suggested^{282a} to result from a two-stage electrode process, but is now considered good evidence for different conformations of the two acetyl groups (47, R=H). The second $E_{1/2}$ value corresponds very closely to that observed for 2-acetylpyrrole (48).^{282, 282b} Similar values are reported for the 1-methyl derivatives.^{282a, 282b} This work has been supported to a limited extent by dipole moment studies and by IR spectral measurements (see Sections III, A, 2 and III, B, 2).



R = H	-1.031 volts	-1.65 volts	-1.646 volts
R = Me	-1.053 volts	-1.685 volts	-1.700 volts

The facile polarographic reduction of both α - and β -nitropyrroles^{237a, 291-296} has been utilized in the analysis of the nitration products of pyrrole and its derivatives. It has been possible not only to identify the products by this method but also to determine the isomer ratios.²⁹⁴⁻²⁹⁶

Sulfonation products can be analyzed in a similar way. The method differs, however, in one significant aspect, in that the sulfonic acids are not polarographically reducible but are readily oxidized in acidic media.³⁰⁰ As was noted for the acyl and nitro compounds, the α -

²⁸⁷ N. Tyutyulkov and I. Bakyrzhiev, *Compt. Rend. Acad. Bulgare Sci.* **12**, 133 (1959); *Chem. Abstr.* **54**, 11804 (1960).

²⁸⁸ E. Laviron, M. Person, and P. Fournari, *Compt. Rend.* **255**, 2440 (1962).

²⁸⁹ M. Dezelic, A. Lackovic, and M. Trkovnik, *Croat. Chem. Acta* **32**, 31 (1960); *Chem. Abstr.* **54**, 13902 (1960).

³⁰⁰ A. P. Terent'ev, L. A. Yanovskaya, and E. A. Terent'eva, *Dokl. Akad. Nauk SSSR* **70**, 649 (1950); *Chem. Abstr.* **44**, 4898 (1950).

sulfonic acids react more readily. The $E_{1/2}$ values lie in the range 0.015–0.026 volts for the 2-sulfonic acids, whereas the 3-sulfonic acids are less readily oxidized with $E_{1/2}$ values of *ca.* 0.05 volts.^{300, 301}

Some attempts have been made in recent years to put the steric and electronic effects of substituents on a more quantitative basis (for a review, see Zuman²⁷⁵).

From the results already given, it can be seen that the ease of polarographic reduction depends on the ring position of the reducible group and also on the positions and electronic nature of other substituents. It was readily shown that the polar effects of the substituents on the half-wave reduction potentials could be expressed in the general form of the Hammett equation.

$$\Delta E_{1/2} = \rho \sigma_X$$

In this equation $\Delta E_{1/2}$ is the shift in half-wave potential as a result of the introduction of the substituent X in place of hydrogen, ρ is the reaction constant, and σ_X is the total polar substituent constant. For pyrrole systems, where it is only the substituent that is reduced, the ring being nonreducible, the equation is modified^{275, 276} to

$$\Delta E_{1/2} = \rho_{\pi, \text{het.R}} \sigma_{\text{het.X}}$$

In this equation the substituent constant $\sigma_{\text{het.X}}$ refers specifically to the substituent attached to the heterocyclic ring and its value depends not only on the nature of the substituent, but also on its position with respect to both the reducible group and the heteroatom. It will also depend upon the type of heterocyclic system. The reaction constant $\rho_{\pi, \text{het.R}}$ describes the ease of reduction of the substituent R and will vary with the type of heterocyclic system and the position of the substituent R with respect to the heteroatom. Because of the limited number of known $\sigma_{\text{het.X}}$ values, it is more convenient to use σ values derived from benzene systems and it has been shown that σ_{para} values may be used for substituent effects across the 2,5-positions and σ_{meta} values for substituent effects across the 2,4-(3,5)positions.³⁰² Using the equation

$$\Delta E_{1/2} = \rho_{\pi, \text{het.R}} \sigma_X$$

a comparison of $\rho_{\pi, \text{het.R}}$ and $\rho_{\pi R}$ for benzene derivatives shows that

³⁰¹ A. P. Terent'ev, L. A. Yanovskaya, and E. A. Terent'eva, *Zh. Obshch. Khim.* **22**, 859 (1952); *Chem. Abstr.* **47**, 3294 (1953).

³⁰² J. Tirouflet and E. Laviron, *Ric. Sci.* **29**, 189 (1959).

the pyrrolyl derivatives are more readily reduced than the corresponding benzene compounds.^{303, 304} The ratio $\rho_{\pi, \text{het. R}}/\rho_{\pi \text{R}}$ is of the order 1.7^{305, 305a} to 2.1³⁰⁶ suggesting the greater ability of pyrrole to transmit electronic effects. The half-wave potential for iodopyrrole, however, is reported to be similar to that of iodobenzene indicating the comparable ease of reductive elimination of the iodine.³⁰⁷ The effect of substituents on the polarographic reduction of acyl pyrroles is best expressed by a modified Taft equation.²⁷⁵

$$\Delta E_{1/2} = \rho_{\pi, \text{het.}}^* \sigma_{\text{CH}_3\text{X}}^*$$

Using polarographic data it has also been possible to estimate the "heteroatom effect" on the reaction rates in terms of a σ constant related to the effect of the heterocyclic ring. The constant σ for benzene is taken as zero and, for a given reducible group, $\rho_{\pi, \text{het. R}}$ is approximately equal to $\rho_{\pi \text{R}}$. Using this technique a wide range of σ values was obtained depending on the reduction process. Using polarographic measurements, σ values ranging from -1.14 to -0.07 were obtained^{285, 292, 303-305a} for an NH group replacing the C-2-C-3 link of a monosubstituted benzene (i.e., a measure of the "heteroatom effect" for the 2-pyrrolyl ring), with an average value of -0.70 , and a range of -2.00 to -1.27 , with an average value of -1.68 , for the corresponding replacement of the C-3-C-4 link.^{291, 305} These values compare in relative order and size with those obtained by pK_a measurements of 2- and 3-pyrrolylcarboxylic acids.²³⁹ The values calculated for the 2-pyrrolyl system are closely similar to the σ value of -1.44 obtained spectroscopically for the "heteroatom effect" of an *N*-methyl group replacing the C-2-C-3 link of a monosubstituted ring.^{305a}

4. Mass Spectra

a. *Pyrrole and Alkyl Pyrroles.* The diagnostic use of mass spectral data has been reported for the structural elucidation of several

³⁰³ J. Nakaya, H. Kinoshita, and S. Ono, *Nippon Kagaku Zasshi* **78**, 935 (1957); *Chem. Abstr.* **53**, 21277 (1959).

³⁰⁴ J. Tirouflet and M. Person, *Ric. Sci.* **30**, 269 (1960).

³⁰⁵ J. Tirouflet and R. Dabard, *Ric. Sci.* **29**, 211 (1959).

^{305a} S. V. Tsukerman, Y. N. Surov and I. F. Lakruskin, *Zh. Obshch. Khim.* **37**, 364 (1967); *Chem. Abstr.* **67**, 43294 (1967).

³⁰⁶ P. Fournari, Thesis, University of Dijon (1961).

³⁰⁷ E. Gergely and T. Iredale, *J. Chem. Soc.*, 3502 (1951).

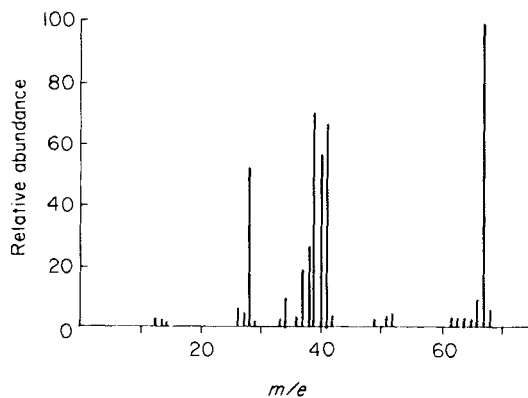


FIG. 3. Mass spectrum of pyrrole.

naturally occurring pyrroles³⁰⁸⁻³¹¹ and an attempt has been made to characterize nitrogen heterocycles, including substituted pyrroles, by the appearance (or otherwise) of specific mass spectral peaks.³¹² However, relatively few publications describe systematic studies of the fragmentation modes of pyrrole and its derivatives.³¹³⁻³¹⁵ Ambiguity may arise in the interpretation of the fragmentation patterns when the mass spectrum is measured under low resolution, for although the fragmentation of pyrrole appears to be similar in many respects to that of furan³¹⁶ and thiophene,^{317, 317a} it is not possible to differentiate between the hydrocarbon fragments and isobaric fragments containing nitrogen. Under conditions of high resolution (Fig. 3), however, it is

³⁰⁸ J. Meinwald and Y. C. Meinwald, *J. Am. Chem. Soc.* **88**, 1305 (1966).

³⁰⁹ S. Hanessian and J. S. Kaltenbronn, *J. Am. Chem. Soc.* **88**, 4509 (1966).

³¹⁰ H. H. Wasserman, G. C. Roberts, and D. D. Keith, *Chem. Commun.* p. 825 (1966).

³¹¹ M. Stoll, M. Winter, F. Gautschi, I. Flamert, and B. Willhalm, *Helv. Chim. Acta* **50**, 628 (1967).

³¹² A. L. Jennings and J. E. Boggs, *J. Org. Chem.* **29**, 2065 (1964).

³¹³ A. M. Duffield, R. Bengelmans, H. Budzikiewicz, D. A. Lighter, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.* **87**, 805 (1965).

³¹⁴ H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman, and J. M. Wilson, *J. Chem. Soc.* 1949 (1964).

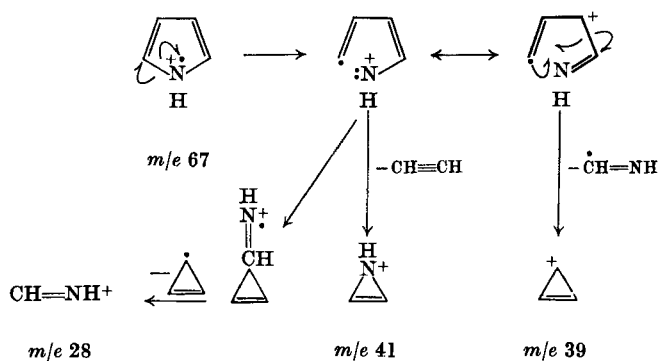
³¹⁵ A. H. Jackson, G. W. Kenner, H. Budzikiewicz, C. Djerassi, and J. M. Wilson, *Tetrahedron* **23**, 603 (1967).

³¹⁶ J. Collin, *Bull. Soc. Chim. Belges* **69**, 449 (1960).

³¹⁷ H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds." Holden-Day, San Francisco, California, 1967.

^{317a} "Catalog of Mass Spectra," Res. Project 44, No. 158. Am. Petrol. Inst., Carnegie Inst. Technol., Pittsburg, Pennsylvania.

readily apparent that, for example, the most abundant fragment peak m/e 39 of pyrrole comprises the ion $C_3H_3^+$ accompanied by less than 1% C_2HN^+ . The mass spectrum of pyrrole has been interpreted in terms of the fragmentation illustrated below (Scheme 1). The parent peak, m/e 67, is the base peak and the most abundant fragment ion is $C_3H_3^+$, most probably the cyclopropenyl ion. Other peaks of relatively high abundance have m/e values of 41, 40, and 28. Whereas the formation of the ion m/e 28 parallels the behavior of furan and thiophene, the $C_3H_4^+$ ion, m/e 40, is not abundant in the spectra of either



SCHEME 1

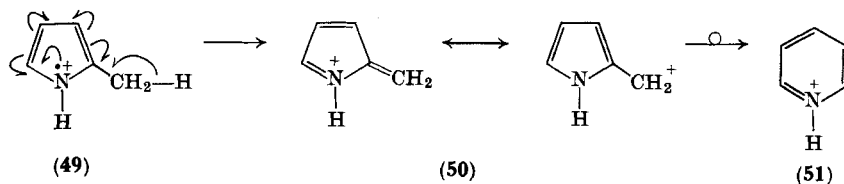
of these compounds and it is considered that the formation of hydrogen cyanide as a stable neutral fragment is the driving force in its production. The fragment $C_2H_2N^+$ also contributes to the intensity of the m/e 40 peak. The peak m/e 41 ($M-CH\equiv CH$) resembles a similar fragmentation of thiophene.

The mass spectra of pyrrole, four *C*-alkyl, and two *N*-alkyl derivatives are to be found in the American Petroleum Institute catalog of mass spectral data.³¹⁸ Other publications report the most abundant fragment peaks of some *N*- and *C*-substituted pyrroles.^{313, 314}

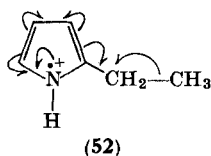
The principal difference in the mass spectra of the *C*-methylpyrroles compared with that of pyrrole is the appearance of the base peak at $M-1$ resulting from the ready loss of a hydrogen radical from the methyl group. The initially formed fragment ion is most probably

³¹⁸ "Catalog of Mass Spectra," Res. Project 44, Nos. 632, 1347, 1418, 1532, 1536, and 1719. Am. Petrol. Inst., Carnegie Inst. Technol., Pittsburg, Pennsylvania.

the azafulvene ion (50), which, by analogy with the rearrangement of the benzyl ion to the tropylium ion,³¹⁹ is thought to undergo ready conversion into the pyridinium ion (51) (see later). An alternative fragmentation to give $M - \text{CH}_3$ occurs to a negligible extent and ions

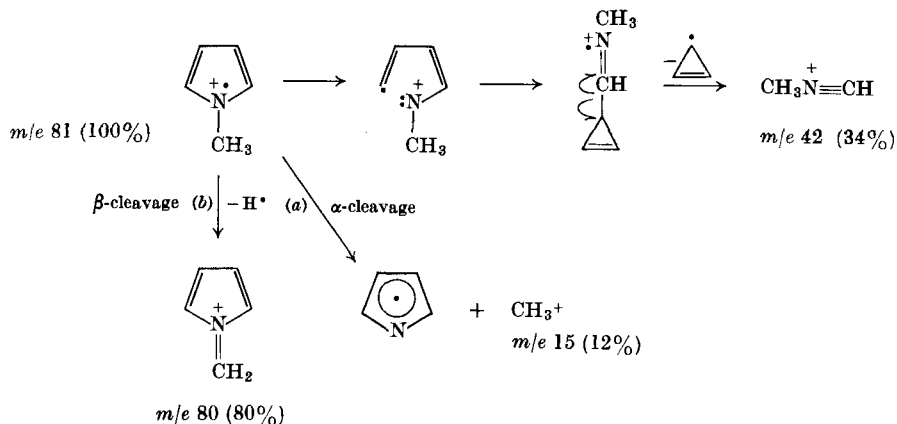


resulting from further fragmentation of the pyridinium ion are of relatively low abundance. Although the mode of fragmentation of other *C*-alkylpyrroles is similar to that of the *C*-methyl compounds, the observed spectra differ considerably. The base peak is still the azafulvene or pyridinium ion, but as it results from β -cleavage of the alkyl group its position relative to that of the parent peak depends on the length of the alkyl group. Thus, the base peak of ethylpyrroles is $M - 15$ (52 \rightarrow 51) and there is little further fragmentation. The



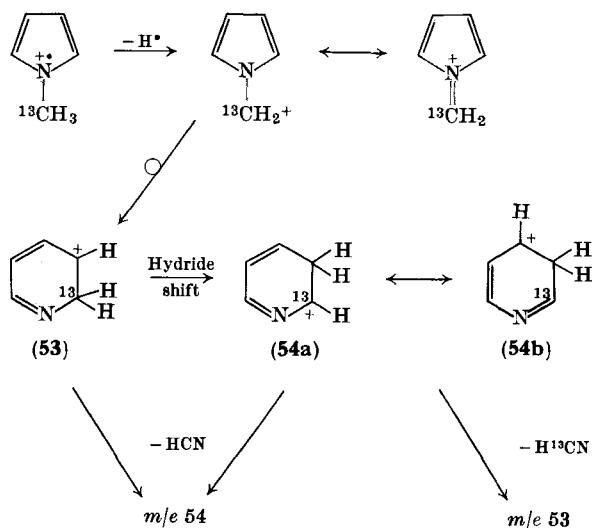
behavior of *N*-alkylpyrroles is somewhat different from that of the *C*-alkyl compounds. For, although the $M - 1$ peak is very strong in the mass spectrum of 1-methylpyrrole, it is the molecular ion m/e 81 that produces the base peak. The fragment ion m/e 15, which is almost certainly attributable to CH_3^+ , is also quite large. Fragmentation of the molecular ion gives a large peak corresponding to mass 42, $\text{HC}\equiv\text{NMe}$, by an analogous cleavage to that which produces the fragment ion $\text{HC}\equiv\text{NH}$ from pyrrole. The prominent $M - 1$ ion produced by hydrogen cleavage from the methyl group may be represented either as the immonium ion or pyridinium ion corresponding to the analogous ion from the *C*-methylpyrroles (Scheme 2). The ready expulsion of HCN, characteristic of pyridine systems, supports

³¹⁹ S. Meyerson and P. N. Rylander, *J. Chem. Phys.* **27**, 901 (1957).



SCHEME 2

the postulated rearrangement and an examination of the mass spectrum of 1-methyl- ^{13}C -pyrrole³²⁰ shows that two fragment ions result from the expulsion of HCN from the $M-1$ fragment ion. However, the ratio of labeled to unlabeled fragment ion corresponding to

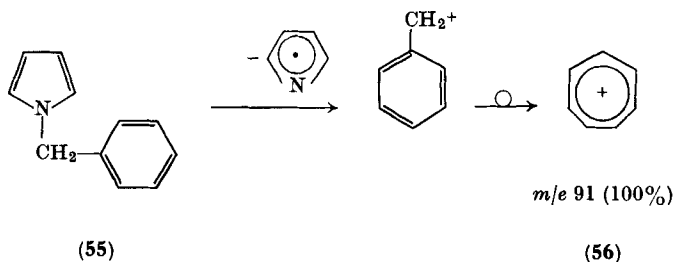


SCHEME 3

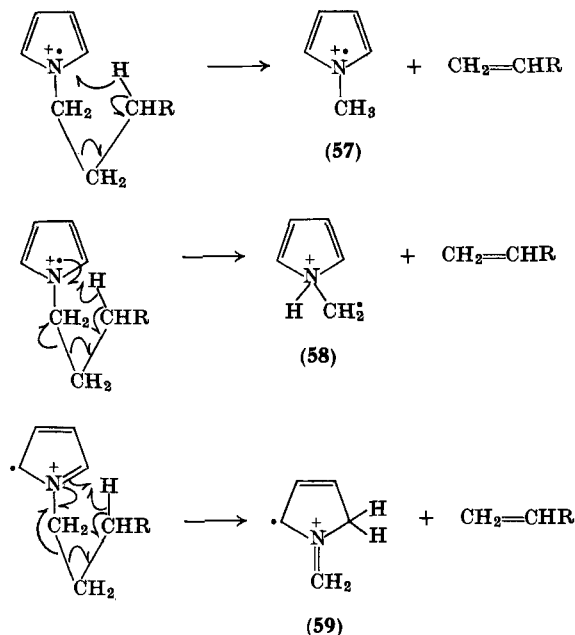
³²⁰ M. Marx and C. Djerassi, *J. Am. Chem. Soc.* **90**, 678 (1968).

mass $M - H - HCN$ is 2:1 compared with the expected 1:1 ratio from the rearrangement of the immonium ion to give the symmetrical pyridinium ion (51). This indicates the possibility of at least two pathways. It has been suggested³²⁰ that the observed predominance of the fragment ion m/e 54 results from the initial formation of the unsymmetrical ion (53) which by loss of HCN yields the fragment ion m/e 54, but which also, by hydride shift, gives the resonance-stabilized ion (54a \leftrightarrow 54b). This ion can undergo the loss of either labeled or unlabeled HCN to give fragment ions m/e 54 and m/e 53 (Scheme 3).

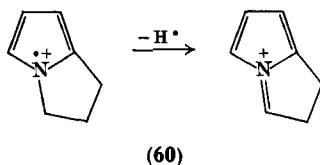
The base peak of *N*-benzylpyrrole is attributable to the tropylium ion (56, m/e 91) resulting from cleavage corresponding to that of route (a) for methylpyrrole (Scheme 2). The alternative cleavage involving the formation of the immonium ion and a phenyl radical occurs to a much lesser extent (9.7%).



The high-resolution mass spectra of other *N*-alkylpyrroles and their deuterium-labeled derivatives have been measured.³¹³ The most abundant ions occur at m/e 80 and 81. It has been shown for *N*-*n*-butyl- and *N*-*n*-pentylpyrrole that the ion of mass 80 is the immonium ion. This peak is shifted two mass units in the spectra of the 1,1-dideuterioalkyl compounds providing confirmation of its structure. However, its origin is twofold. The presence of a metastable peak at m/e 79.2 indicates that part of the m/e 80 peak arises from the loss of a hydrogen atom from the ion of mass 81. This ion constitutes the base peak in the spectra of *N*-*n*-butyl- and *N*-*n*-propylpyrrole and the peak has been shown to contain only the $C_5H_7N^+$ ion for which three possible structures have been suggested (57, 58, and 59). The formation of these ions has been rationalized in terms of the fragmentation shown in Scheme 4. Similarly, fragmentation of pyrrolo[1,2a]pyrrolidine (60) gives a base peak at m/e 106 corresponding to the stable



SCHEME 4

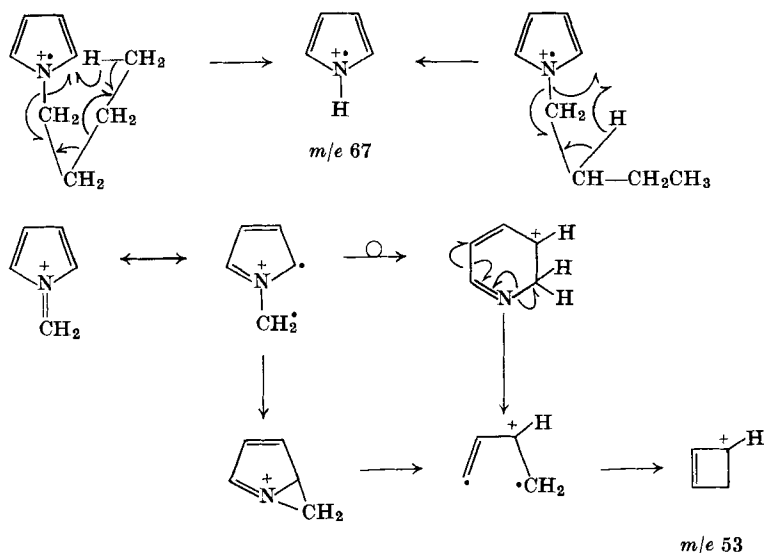


immonium ion.³²¹ Deuterium labeling of the various positions of the *N*-alkyl group confirms that although hydrogen atom migration from C-3 predominates, the hydrogen atom may also originate from C-2 and C-4. Further evidence for these rearrangements was obtained from the spectra of the alkyl pyrroles labeled with deuterium in the ring positions.

A significant fragmentation mode of the *N*-alkylpyrroles produces an ion of mass 67 which is almost homogeneous and corresponds to $C_4H_5N^+$. Deuterium labeling has established that this ion arises predominantly by hydrogen migration either from C-4 of the alkyl

³²¹ R. G. Cooks, F. L. Warren, and D. H. Williams, *J. Chem. Soc., C* 286 (1967).

group with a simultaneous expulsion of two molecules of ethylene, or from C-2 with the expulsion of butene (Scheme 5). Another fragment ion of relatively high abundance is to be found in the mass spectra of all *N*-alkylpyrroles at m/e 53. The peak has been shown to be homogeneous, having the composition $C_4H_5^+$ and is thought to originate from the expulsion of the stable hydrogen cyanide molecule from the fragment ion of mass 80.



SCHEME 5

The fragmentation of *N*-*t*-butylpyrroles³²² appears to be contrary to that observed for other *N*-alkylpyrroles. The formation of an immonium ion from the molecular ion would require elimination of a methyl radical. This cleavage is not observed but a fragment ion resulting from loss of isobutene is formed instead. The exact mechanism of this cleavage is not known.

b. *Acyl Pyrroles and Pyrrolylcarboxylic Esters.* As is the case for many other acylaromatic compounds, the predominant fragmentation of acyl pyrroles results in the formation of acylium ions. Thus, 2-formylpyrrole gives a strong $M - 1$ peak, the molecular ion being the

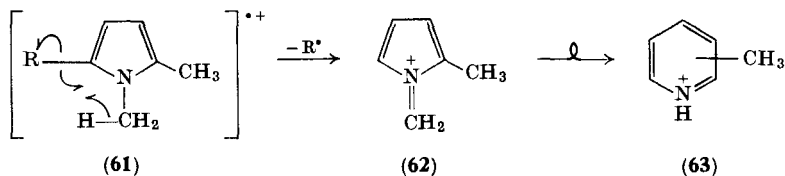
³²² A. Padwa, R. Gruber, D. Pashayan, M. Bursey, and L. Dusold, *Tetrahedron Letters* 3659 (1968).

The fragmentation of the pyrrolyl cation to give the cyclopropenyl ion accounts for the peak at mass 39 (cf. Scheme 1).

The principal fragmentation mode of pyrrolylcarboxylic ethyl esters are shown in Scheme 6. There is a very close similarity between the fragmentations (i), (ii), and (iii) and the principal modes of cleavage of ethyl benzoate.^{323, 324} The base peak corresponds to the cleavage of the ethoxyl group from the molecular ion [fragmentation (ii)], but, also of high abundance (90%) is the peak at m/e 93 [fragmentation (iv)]. This involves the elimination of a molecule of ethanol. The absence of the peak from the mass spectrum of the *N*-methyl derivative indicates that the hydrogen atom originates from the NH group. Although the data are not available, it is most probable that this type of cleavage would be missing from the mass spectrum of ethyl pyrrole-3-carboxylate. By analogy with the fragmentation of acyl pyrroles, the formation of the pyrrolyl cation, m/e 66, may be considered to be, at least in part, a two-step process involving the loss of carbon monoxide from the acylium ion from fragmentation (ii) and consequently the fragmentation mode is more important with the 2-esters than with the 3-esters. The pyrrolyl cation fragments further in the predictable manner to give the cyclopropenyl ion, m/e 39, in high abundance (44%). Formulation of the ion of mass 65 from fragmentation (v) is uncertain; a highly speculative assignment has suggested that it is the cyclopropenyl cyanide cation.³¹⁴

Methyl esters behave like the corresponding ethyl esters with the predictable omission of the peak at m/e 111 and, as expected, the mass spectra of benzyl esters are dominated by the tropylium ion peak.

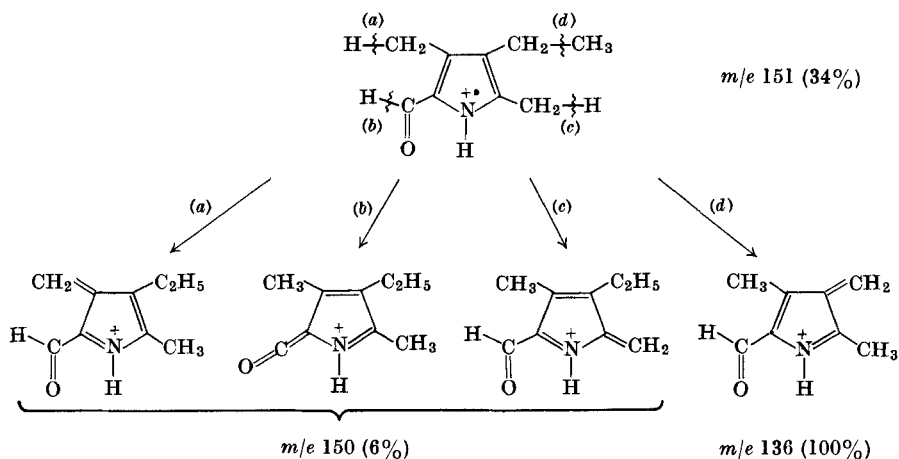
c. *Polysubstituted Pyrroles*. The majority of the mass spectra of polysubstituted pyrroles have been measured at low resolution. It appears, however, that in general the basic fragmentation modes described for the monosubstituted pyrroles also occur for polysubstituted compounds, but in certain circumstances apparently



³²³ F. W. McLafferty and R. S. Gohlke, *Anal. Chem.* **31**, 2076 (1959).

³²⁴ E. M. Emery, *Anal. Chem.* **32**, 1495 (1960).

abnormal cleavage occurs; thus, the major fragmentation of 1,2-dimethyl-5-vinyl- and 5-ethyl-1,2-dimethylpyrrole (**61**, R = vinyl or ethyl) involves the formation of the methylazafulvene cation via hydrogen transfer with simultaneous elimination of the vinyl or ethyl groups, respectively. The exact structure of the expelled radical is uncertain, but the driving force is presumably the formation of the immonium ion (**62**) which can readily rearrange to give the methylpyridinium ion (**63**).

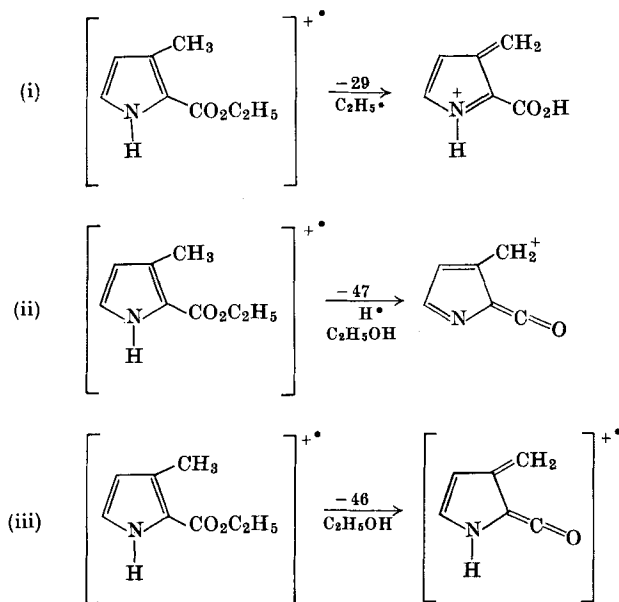


SCHEME 7

With the possibility of competing fragmentation modes, peaks that have a relatively high abundance in the mass spectra of the monosubstituted compounds are often insignificant for the polysubstituted pyrroles in which an alternative cleavage takes precedence and inhibits further fragmentation. Thus, in contrast to mass spectra of formyl- and methylpyrroles in which the $M - 1$ peaks are of high relative abundance, the base peak of 3-ethyl-5-formyl-2,4-dimethylpyrrole occurs at $M - 15$, resulting from β -cleavage of the ethyl group, and the $M - 1$ peak is small (Scheme 7).

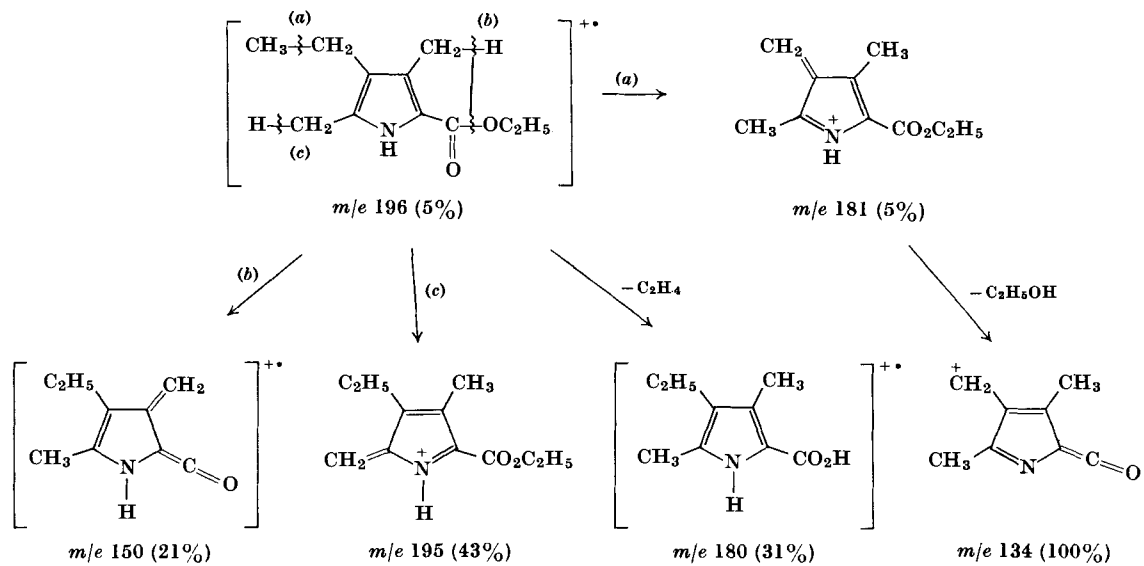
The mass spectra of ethyl polymethylpyrrole carboxylates are little affected by the orientation of the methyl groups and ester groups. Peaks resulting from fragmentations of the type shown in Scheme 6 remain unchanged in their relative size, but the relative abundance of the peaks originating from fragmentation modes in which the methyl

groups are involved (see Scheme 8) depend on the relative orientation of the methyl and ester groups. Thus, the appearance of peaks originating from fragmentation modes (i) and (ii) depends on the presence of the methyl group adjacent to the ester group. Fragmentation (ii) may be a two-step process via fragmentation (i) followed by elimination of water. The loss of ethanol in fragmentation (iii) will also be governed to some extent by the presence of the adjacent methyl group, but this process may also involve other hydrogen atoms, as, for example, fragmentation (iv) in Scheme 6. It becomes increasingly evident that

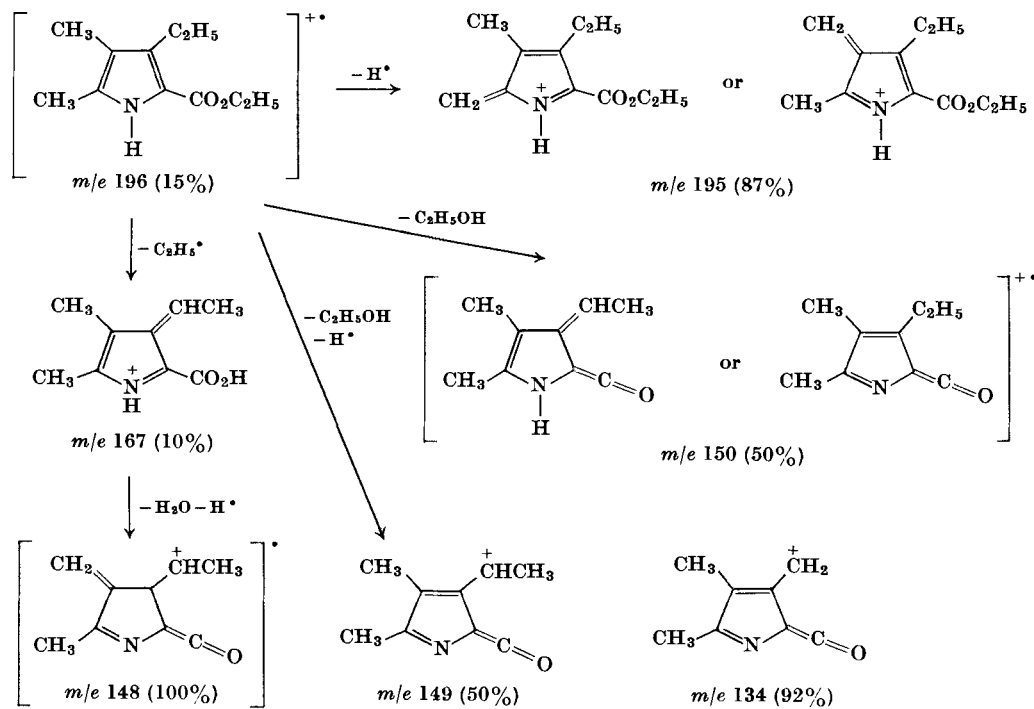


SCHEME 8

the presence of an ethyl group in the pyrrole nucleus fundamentally changes the fragmentation pattern. In the majority of cases β -cleavage of the ethyl group is of considerable importance, giving the ion of mass $M - 15$. However, this ion is often only a precursor to further fragmentation involving the ester group producing a more stable ion which is observed as the base peak. The major fragmentation modes of ethyl 3-ethyl-2,4-dimethylpyrrole-5-carboxylate are given in Scheme 9. In general, fragmentation which produces ions which are



SCHEME 9



SCHEME 10

resonance stabilized between the 2- and 4-positions will take precedence over cleavage in which the resonance stabilization is between positions 2 and 3 or 2 and 5. By contrast the fragmentation pattern of the isomeric ethyl 3-ethyl-4,5-dimethylpyrrole-2-carboxylate is shown in Scheme 10. The $M - 15$ peak is completely absent. The base peak is found at m/e 148 ($M - 48$) and it has been suggested that it originates from a two-step fragmentation of the molecular ion analogous to fragmentation modes (i) and (ii) of Scheme 8 (i.e., $M - C_2H_5 - H - H_2O$). The fragment ion of mass 134 could be derived via several different cleavage routes. The predominance of the ions of mass 148 and 134 has been rationalized in terms of resonance stabilization between the 2- and 3-positions, but equally possible is rearrangement to the pyridinium ions.

The behavior of pyrroles having more than one ester group or both ester and acyl groups has also been studied. In general the patterns already discussed are followed, the predominant peaks being those in which there is resonance stabilization of the fragment ion between the 2- and 4-positions.

B. SPECTROSCOPIC MEASUREMENTS

1. IR and Raman Spectra

a. *Fundamental Vibrations of Pyrrole.* The IR^{107, 110, 123, 325-334} and Raman spectra³³⁵⁻³⁴² of pyrrole have been studied extensively during the past 60 years. The early work on the Raman effect was later supplemented by IR spectral data and assignments were made¹²³

³²⁵ W. W. Coblentz, "Investigation of Infrared Spectra," Part I. Carnegie Inst. Wash., Washington, D.C., 1905.

³²⁶ R. Manzoni-Ansidei and M. Rolla, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **27**, 410 (1938); *Chem. Abstr.* **32**, 8933 (1938).

³²⁷ J. Lecomte, *Bull. Soc. Chim. France* 415 (1946).

³²⁸ J. Garach and J. Lecomte, *Compt. Rend.* **222**, 74 (1946).

³²⁹ P. Mirone and A. M. Drusiani, *Atti Acad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **16**, 69 (1954); *Chem. Abstr.* **48**, 9196 (1954).

³³⁰ P. Mirone and C. Bonino, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **17**, 250 (1954); *Chem. Abstr.* **49**, 15488 (1955).

³³¹ W. Otting, *Chem. Ber.* **86**, 1079 (1956).

³³² J. Morecillo and J. M. Orza, *Anales Real Soc. Españ. Fis. Quim. (Madrid)* **B56**, 231 and 253 (1960); *Chem. Abstr.* **54**, 19162 (1960).

³³³ A. M. Prima, *Opt. i Spektroskopiya, Akad. Nauk SSSR, Otd. Fiz.-Mat. Nauk, Sb. Statei* **3**, 157 (1967); *Chem. Abstr.* **67**, 77602 (1967).

³³⁴ J. Loisel and V. Lorenzelli, *Spectrochim. Acta* **23**, 2903 (1967).

for twenty-four normal vibrational modes (Fig. 4). Because of molecular interaction in liquid pyrrole, the frequencies of several modes differ significantly for liquid and vapor phase spectra, notably the N-H-stretching mode (see Section II,B) and the vibrational modes of the B_2 species. The comparative studies by Lord and Miller¹²³ of the Raman and IR spectra in the liquid phase of pyrrole and deuterated pyrroles (Table XIV) using frequency product ratios^{343, 344} favored the planar structure of C_{2v} symmetry for pyrrole, although a nonplanar C_s structure was not rigorously excluded. The pseudo D_{5h} symmetry point group has been excluded by a consideration of the polarization of the Raman bands.^{339a} Lecomte,³²⁷ working without the full knowledge of the work of Lord and Miller, also arrived at the conclusion that pyrrole has C_{2v} symmetry and the assignments given in Fig. 4 and Table XIV are based on pyrrole being of this point group. The planar structure was finally confirmed by microwave spectral data.^{19, 20}

Despite the extensive investigation of the vibrational spectra, several correlations remain in doubt. Mirone¹⁰⁷ measured the IR spectrum of pyrrole in both the liquid and gaseous phase. A considerable number of the assignments made by Lord and Miller were essentially confirmed by Mirone, but he suggested the alternative correlation of the band near 1582 cm^{-1} for the vibrational mode ν_6 . Also, from a consideration of the band profiles in the gaseous phase the assignments of the vibrational modes ν_{10} and ν_{20} made by Lord and

³³⁵ S. Venkateswaren, *Indian J. Phys.* **5**, 145 (1930).

³³⁶ G. B. Bonino, R. Manzoni-Ansidei, and P. Pratesi, *Z. Physik. Chem.* **B22**, 21 (1933).

³³⁷ G. B. Bonino and R. Manzoni-Ansidei, *Ric. Sci.*, Suppl. **7**, 510 (1936).

^{337a} G. B. Bonino and R. Manzoni-Ansidei, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **25**, 494 (1937); *Chem. Abstr.* **31**, 8377 (1937).

³³⁸ A. Stern and K. Thalmeyer, *Z. Physik. Chem.* **B31**, 403 (1936). For criticism of this work, see G. B. Bonino, *Gazz. Chim. Ital.* **66**, 316 (1936) and G. B. Bonino and R. Manzoni-Ansidei, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **25**, 489 (1937); *Chem. Abstr.* **31**, 8377 (1937).

³³⁹ A. W. Reitz, *Z. Physik. Chem.* **B33**, 179 (1936).

^{339a} A. W. Reitz, *Z. Physik. Chem.* **B38**, 275 (1937).

³⁴⁰ O. Redlich and W. Stricks, *Monatsh. Chem.* **68**, 47 (1936).

³⁴¹ R. Manzoni-Ansidei, *Ric. Sci.* **10**, 328 (1939).

³⁴² N. K. Sidorov and L. P. Kalashinokova, *Opt. i Spektroskopiya* **24**, 469 (1968); *Chem. Abstr.* **68**, 118309 (1968).

³⁴³ O. Redlich, *Z. Physik. Chem.* **B28**, 371 (1935).

³⁴⁴ F. Halverson, *Rev. Mod. Phys.* **19**, 87 (1947).

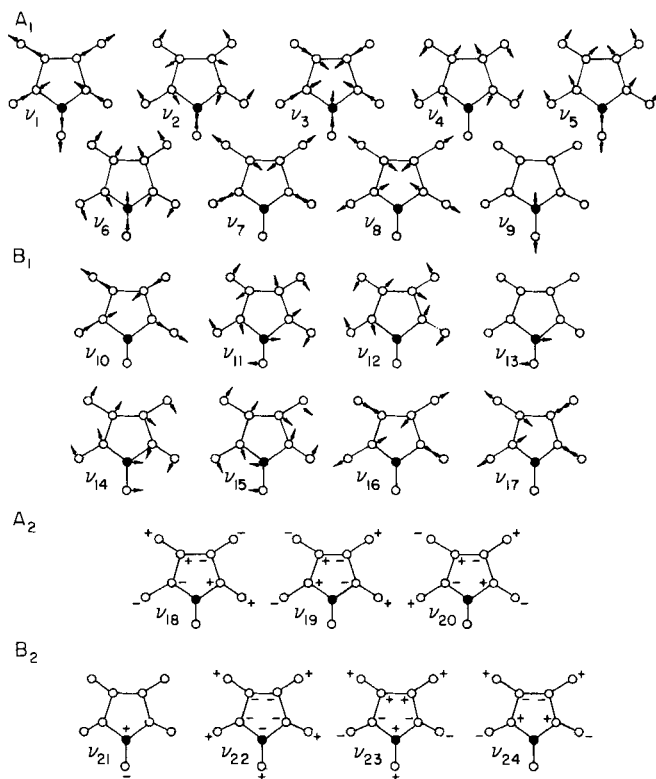


FIG. 4. Fundamental vibrational modes of pyrrole.

Miller were reversed. It was suggested that the absorption near 1470 cm^{-1} , originally assigned by Lord and Miller to vibrational mode ν_6 , was an overtone of the symmetrical CH out-of-plane deformation ν_{22} . Morcillo and Orza³³² supported the reversal of the assignments made by Mirone for vibrational modes ν_{10} and ν_{20} but reestablished the band near 1470 cm^{-1} as a fundamental vibrational mode. They further reversed the assignments for the vibrational modes ν_{16} and ν_{17} and suggested the alternative correlations of the bands at 838 and 618 cm^{-1} to the vibrational modes ν_{24} and ν_{18} . They also assigned the band near 649 cm^{-1} to the vibrational mode ν_{23} .

The position of the symmetrical ring-breathing frequency, ν_3 , is also in some doubt. This vibrational mode would be IR-inactive for a molecule of D_{5h} symmetry and only weakly active for a molecule of

TABLE XIV
IR AND RAMAN SPECTRA OF PYRROLE AND DEUTERATED DERIVATIVES IN LIQUID PHASE^a

Pyrrole		Pyrrole-1- <i>d</i>		<i>sym</i> -Pyrrole- <i>d</i> ₄		Pyrrole- <i>d</i> ₅		Class ^b	Band assignment ^c
Raman	Infrared	Raman	Infrared	Raman	Infrared	Raman	Infrared		
3400	3410	2525	2534	3410	3400	2535	2530	A ₁	ν ₉ NH stretching vibration
3133	3133	3131	3135	2358	2358	2350	2369	A ₁	ν ₈ CH stretching vibration
3133 ^d	3133 ^c	3131 ^d	3135 ^c	2358 ^d	2358 ^c	2368	2369 ^c	B ₁	ν ₁₇ CH stretching vibration
3111	3108 ^c	3104	3106 ^c	2309	2307 ^c	2309	2305 ^c	B ₁	ν ₁₆ CH stretching vibration
3100	3108	3104 ^d	3106	2309 ^d	2339	2309 ^d	2348	A ₁	ν ₇ CH stretching vibration
		2709							ν ₄ + ν ₆
(Bands in the region 2000–1600 cm ⁻¹ are not well documented.)									
1528	1531	—	1532	1463	1468	1455	—	B ₁	ν ₁₅ Ring-stretching mode
1484	—								ν ₁₀ + ν ₂₃
1468	1466	1465	1464	1401	1401	1389	1389	A ₁	ν ₆ Ring-stretching mode
		—	1428						ν ₁₃ + ν ₁₈
—	1418	—	1418	—	1415	1413	1415	B ₁	ν ₁₄ Ring-stretching mode
1379	1384	1384	1384	1319	1318	1317	1318	A ₁	ν ₅ Ring-stretching mode
		1350	1354			—	1341		3 × ν ₂₁
		—	1290						ν ₂₁ + ν ₂₃
—	1289	1210	—	—	1111	—	1131		2 × ν ₁₀
						1211	1210		ν ₂₀ + ν ₂₁ or ν ₁ + ν ₁₉
1237	—	1237	—	917	920	909	910	A ₁	ν ₄ CH in-plane deformation
						1145	1147		2 × ν ₂₂ or ν ₁ + ν ₂₁
1144	—	1135	—	1094	1093	1084	1085	A ₁	ν ₃ Ring-breathing mode
1144 ^d	1146	—	915	—	1163	892	893	B ₁	ν ₁₃ NH in-plane deformation
			1116						
				—	1027	—	1025		2 × ν ₁₉
1076	1076	1074	1074	—	812	—	813	A ₁	ν ₂ CH in-plane deformation
1045	1047	—	1026	—	872	—	852	B ₂	ν ₂₄ CH out-of-plane deformation

1045 ^d	1047 ^d	—	1048	848	849	808	—	B ₁	ν_{12} CH in-plane deformation
1015	1015	1010	1015	—	793	—	789	B ₁	ν_{11} CH in-plane deformation
		—	1220	953	956	—	961		$\nu_{19} + \nu_{21}$
									$\nu_{18} + \nu_{19}$
									$\nu_6 - \nu_{21}$
880	884			—	899		943		$\nu_{15} - \nu_{10}$
		911	905						$2 \times \nu_{21}$
866	869 ^e	869	870	769	—	766	—	A ₂	ν_{20} CH out-of-plane deformation
837	839 ^e	831	835	730	—	728	—	B ₂	ν_{23} Ring-out-of-plane deformation
		—	808						$\nu_{14} - \nu_{10}$
		—	786						$\nu_4 - \nu_{21}$
		780	783						$\nu_5 - \nu_{10}$
—	768 ^e	—	766					B ₂	ν_{22} CH out-of-plane deformation
711		708		692		693		A ₁	ν_1 Ring in-plane deformation
711 ^d		708 ^d		514		516		A ₂	ν_{19} CH out-of-plane deformation
647	652 ^e	606		560		565		B ₁	ν_{10} Ring in-plane deformation
618 ^e									$\nu_5 - \nu_{22}$
565	561	450		560 ^d		450		B ₂	ν_{21} NH out-of-plane deformation
510 ^{e,f}		510 ^f		440 ^f		440 ^f		A ₂	ν_{18} Ring out-of-plane deformation

^a Data given in cm⁻¹. The frequencies and the numbering of the vibrational modes are according to Lord and Miller.¹²³ Absorption data for the region above 3000 cm⁻¹ taken from the work of Morcillo and Orza.³³²

^b The vibrational class is given for a molecule of point group C_{2v} .

^c No reasonable assignment can be made for the following absorption bands: pyrrole, 844 cm⁻¹; pyrrole-1-*d*, 1126 cm⁻¹; *sym*-pyrrole-*d*₄, 1178, 1147, 1058, 931, and 830 cm⁻¹; and pyrrole-*d*₅, 2679, 1442, 1058, and 1039 cm⁻¹.

^d Band used twice.

^e See text.

^f Calculated frequencies using the product rule.

C_{2v} symmetry which approximates closely to one of D_{5h} symmetry. For the unsubstituted pyrrole ring an intense and highly polarized band was observed in the Raman spectrum at 1145 cm^{-1} and was assigned to the ring-breathing mode. However, a band is also observed at 1146 cm^{-1} in the IR spectrum. It was suggested that this band originated from the N-H in-plane bending mode.¹²³ Support for these assignments was obtained from deuteration studies.¹²³ The IR band at 1146 cm^{-1} shifted to 915 cm^{-1} on *N*-deuteration, whereas the Raman band near 1140 cm^{-1} remained and a new band was observed at 911 cm^{-1} .

The CH stretching modes of pyrrole have been studied in detail^{345, 346} and attempts were made to correlate their frequencies with the electron distribution in the ring.

Considerable interest has also been shown in the NH vibrational modes, particularly in connection with hydrogen bonding and molecular association. The frequency and integrated intensity of the NH stretching vibration in nonpolar solvents relative to that observed in the vapor phase is consistent with the Kirkwood-Bauer-Magat relationship,^{105, 347} but where a strong interaction exists between the solvent and the pyrrole molecule a large deviation from the expected value occurs (see Section II, B).

A comparative study of the frequencies and intensities of the NH and ND stretching vibrations has shown that there is virtually no coupling with the CH or ring vibrations,³⁴⁸ but there does appear to be evidence for interaction of the NH in-plane deformation with CH in-plane deformations. This was shown by comparative studies¹²³ of the spectra of pyrrole and pyrrole-1-*d*, in the region $1100\text{--}800\text{ cm}^{-1}$ and also from comparative studies of pyrrole, thiophene, furan, and *ortho*-disubstituted benzenes.³⁴⁹⁻³⁵¹ At high concentrations of pyrrole in most nonpolar solvents two absorption bands are observed in the region $3500\text{--}3400\text{ cm}^{-1}$. Both bands are assigned to the NH stretching mode. The intensity of the lower frequency band decreases on

³⁴⁵ J. M. Lebas and M. L. Josien, *Bull. Soc. Chim. France* 251 (1957).

³⁴⁶ R. Joeckle, E. Lemperle, and R. Mecke, *Z. Naturforsch.* **22A**, 395 (1967).

³⁴⁷ G. Lévi, *Compt. Rend.* **B263**, 493 (1966).

³⁴⁸ M. T. Forel, J. P. Leickmann, and M. L. Josien, *J. Chim. Phys.* **57**, 1103 (1960).

³⁴⁹ B. Bak, S. Brodersen, and L. Hansen, *Acta Chem. Scand.* **9**, 749 (1955).

³⁵⁰ G. Waddington, J. W. Knowlton, D. W. Scott, G. D. Oliver, S. S. Todd, W. N. Hubbard, J. C. Smith, and H. M. Huffman, *J. Am. Chem. Soc.* **71**, 797 (1949).

³⁵¹ A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* 3670 (1959).

decreasing the concentration of the solution and this band has been assigned to a dimeric system (see, for example, Mirone¹⁰²). However, even at extremely low concentrations a second absorption band close to the main absorption band near 3500 cm^{-1} and approximately one-twentieth of its intensity has been detected by several investigators.^{128a, 159, 159a, 352} Weak satellite bands lying approximately 50 cm^{-1} to the low-frequency side and also roughly one-twentieth of the intensity of the main band have also been observed for the first, second, and third harmonics of the NH stretching fundamental mode.³⁵³⁻³⁵⁸ Pauling³⁵⁴ attributed the main band to the NH stretching vibration of the planar molecule and the weak satellite to the nonplanar molecule in which the imino hydrogen lies out of the plane of the ring. In a study of the spectrum of pyrrole vapor in the third harmonic region, Freymann^{355-355b} observed a three-component absorption band which he attributed to three different molecular species of the pyrrole system. Zumwalt and Badger³⁵⁶ suggested an alternative, and more reasonable, explanation that the satellites arise from excited energy states which do not correspond to different geometrical configurations, as suggested by Pauling,³⁵⁴ but to vibrational excitation. The intensity ratios and also the temperature effect indicate that there is an unusually strong interaction between the NH stretching mode and a vibrational mode which causes absorption near 650 cm^{-1} . The weak absorption which lies approximately 20 cm^{-1} on the low frequency side of the NH fundamental stretching band has been described as a "hot" band by Linnell,³⁵² i.e., the absorption results from a transition in molecules which are in a low-lying energy level above the ground state. From a study of the variation in the relative intensities of the fundamental and "hot" bands with change in temperature, it was suggested that the vibrational mode involved lay in the region $500\text{--}300\text{ cm}^{-1}$. Solvent frequency-shift effects have confirmed that the band near 560 cm^{-1} in the liquid phase, which shifts to 503 cm^{-1} in dilute solution in carbon tetrachloride^{107, 330, 359}

³⁵² R. H. Linnell, *J. Chem. Phys.* **41**, 3274 (1964).

³⁵³ O. R. Wulf and U. Liddel, *J. Am. Chem. Soc.* **57**, 1464 (1935).

³⁵⁴ L. Pauling, *J. Am. Chem. Soc.* **58**, 94 (1936).

³⁵⁵ M. Freymann, *Compt. Rend.* **203**, 721 (1936).

^{355a} M. Freymann, *Compt. Rend.* **205**, 852 (1936).





^{355b} M. Freymann, *Ann. Chim. (Paris)* **11**, 11 (1939).

³⁵⁶ L. R. Zumwalt and R. M. Badger, *J. Chem. Phys.* **7**, 629 (1939).

³⁵⁷ M. L. Josien and N. Fuson, *Compt. Rend.* **232**, 833 (1951).

³⁵⁸ N. Fuson and M. L. Josien, *J. Chem. Phys.* **20**, 1043 (1952).

TABLE XV
IR ABSORPTION BANDS OF MONOSUBSTITUTED PYRROLES

								
	cm ⁻¹	ε	cm ⁻¹	ε	cm ⁻¹	ε	cm ⁻¹	ε
Ring CC-stretching vibrations								
1-Substituted pyrroles	1549 ± 3	(20 ± 5)	1477 ± 7	(105 ± 80)	—	—	1394 ± 10	(25 ± 10)
2-Substituted pyrroles	1558 ± 9	(50 ± 30)	1471 ± 3	(45 ± 25)	1415 ± 8	^b	—	—
3-Substituted pyrroles ^a	ca. 1535	(ca. 260)	ca. 1503	(ca. 115)	ca. 1410	(ca. 145)	ca. 1391	(ca. 85)
CH In-plane deformations								
1-Substituted pyrroles	1069 ± 6	(170 ± 70)	1027 ± 9	(85 ± 50)				
2-Substituted pyrroles	1088 ± 8	(120 ± 70)	1033 ± 6	(180 ± 100)				
3-Substituted pyrroles ^a	ca. 1085	(ca. 65)	ca. 1030	(ca. 40)				
CH Out-of-plane deformations								
1-Substituted pyrroles	—	—	926 ± 4	(80 ± 60)			722 ± 2	(425 ± 50)
2-Substituted pyrroles	961 ± 8	(30 ± 15)	927 ± 1	(25 ± 20)	882 ± 2	^c		
3-Substituted pyrroles ^a	ca. 970	(ca. 40)						

^a Due to the limited data available, only approximate values can be given.

^b (30 ± 10) for saturated substituents and (245 ± 80) for conjugated substituents.

^c (20 ± 5) for saturated substituents and (85 ± 40) for conjugated substituents.

and to 475 cm^{-1} in the vapor phase,¹⁰⁷ is the out-of-plane NH deformation.

b. *Substituted Pyrroles*. The Raman^{170, 171, 271, 336, 338, 359-372} and IR^{165-167, 171-175, 189, 192, 206, 207, 231, 238, 239, 266, 271, 330, 371, 373-396}

- ³⁵⁹ P. Mirone and C. Bonino, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **16**, 69 (1954); *Chem. Abstr.* **48**, 9196 (1954).
- ³⁶⁰ G. B. Bonino, R. Manzoni-Ansidei, and P. Pratesi, *Z. Physik. Chem.* **B25**, 348 (1934).
- ³⁶¹ G. B. Bonino, R. Manzoni-Ansidei, *Mem. Accad. Sci. Ist. Bologna, Classe Sci. Fis. Sez. Sci. Nat.* **1**, 7 (1934); *Chem. Abstr.* **29**, 1712 (1935).
- ³⁶² G. B. Bonino and R. Manzoni-Ansidei, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **22**, 349 (1935); *Chem. Abstr.* **30**, 6647 (1936).
- ³⁶³ G. B. Bonino, R. Manzoni-Ansidei, and D. Dinelli, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **22**, 448 (1935); *Chem. Abstr.* **30**, 6647 (1936).
- ³⁶⁴ R. Manzoni-Ansidei, *Ric. Sci.* **7**, 510 (1936) and **8**, 227 (1937); *Chem. Abstr.* **32**, 4879 (1938).
- ^{364a} G. B. Bonino and R. Manzoni-Ansidei, *Ric. Sci.* **8**, 224 (1937); *Chem. Abstr.* **32**, 4879 (1938).
- ^{364b} R. Manzoni-Ansidei and L. Cavallero, *Ric. Sci.* **8**, 223 and 228 (1937); *Chem. Abstr.* **32**, 4879 (1938).
- ³⁶⁵ R. Manzoni-Ansidei, *Atti Accad. Ital. Rend. Classe Sci. Fis., Mat. Nat.* **1**, 669 (1940); *Chem. Abstr.* **37**, 883 (1943).
- ³⁶⁶ R. Manzoni-Ansidei, *Boll. Sci. Fac. Chim. Ind. Bologna* p. 200 (1940); *Chem. Abstr.* **37**, 313 (1943).
- ³⁶⁷ E. Ghigi and P. Chiorboli, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **10**, 242 (1951); *Chem. Abstr.* **45**, 6930 (1951).
- ³⁶⁸ E. Ghigi and P. Chiorboli, *Boll. Sci. Fac. Chim. Ind. Bologna* **9**, 89 (1951); *Chem. Abstr.* **46**, 9424 (1952).
- ³⁶⁹ P. Chiorboli and F. Morelli-Emiliani, *Gazz. Chim. Ital.* **81**, 906 (1951).
- ³⁷⁰ P. Chiorboli, *Atti Accad. Nazl. Lincei, Rend. Classe Sci. Fis., Mat. Nat.* [8] **12**, 588 (1952); *Chem. Abstr.* **46**, 9424 (1952).
- ³⁷¹ P. Chiorboli, *Ann. Chim. (Rome)* **44**, 88 (1954).
- ³⁷² M. Scrocco and L. Caglioti, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **24**, 429 (1958); *Chem. Abstr.* **53**, 50 (1959).
- ³⁷³ R. A. Jones, *Australian J. Chem.* **16**, 93 (1963).
- ³⁷⁴ R. A. Jones, *Australian J. Chem.* **19**, 289 (1966).
- ³⁷⁵ A. Kreutzberger and P. A. Kalter, *J. Phys. Chem.* **65**, 624 (1961).
- ³⁷⁶ R. A. Jones, *Australian J. Chem.* **18**, 289 (1965).
- ³⁷⁷ R. A. Jones, *Spectrochim. Acta* **23A**, 2211 (1967).
- ³⁷⁸ M. Scrocco, L. Caglioti, and V. Caglioti, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **24**, 316 (1958); *Chem. Abstr.* **62**, 19446 (1958).
- ³⁷⁹ P. Mirone and V. Lorenzelli, *Ann. Chim. (Rome)* **48**, 72 (1958).
- ³⁸⁰ A. F. Mironov, L. D. Miroshnichenko, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* **74** (1965); *Chem. Abstr.* **63**, 4127 (1965).

spectra of substituted pyrroles have been reported by numerous investigators, but only recently has there been any systematic study of the IR spectra. For all substituted pyrroles, usually only three bands are observed in the $1600\text{--}1400\text{ cm}^{-1}$ region which, by analogy with the spectrum of pyrrole are assigned to the ring-stretching modes. The number and position of absorption bands attributable to the CH in- and out-of-plane deformations depend on the number and the orientation of the substituents, and, as in the case of substituted benzenes, can be definitive in the characterization of the substituent orientation.

The frequencies of the ring-stretching vibrations for monosubstituted pyrroles^{373, 374} (Table XV) are independent of the type of substituent, but the intensities of the bands increase with increasing electron-withdrawing ability of the substituent. The strong electron-donating effect of the pyrrole ring causes increased conjugation with the electron-withdrawing substituents and thereby produces larger

- ³⁸¹ G. B. Bonino and P. Mirone, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **17**, 167 (1954); *Chem. Abstr.* **49**, 15488 (1955).
³⁸² P. Mirone, A. M. Drusiani, and V. Lorenzelli, *Ann. Chim. (Rome)* **46**, 1217 (1956).
³⁸³ G. B. Bonino and P. Mirone, *Atti Acad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **23**, 198 (1958); *Chem. Abstr.* **52**, 12556 (1958).
³⁸⁴ M. Scrocco and R. A. Nicolaus, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **22**, 500 (1957); *Chem. Abstr.* **51**, 17455 (1957).
³⁸⁵ U. Eisner and R. L. Erskine, *J. Chem. Soc.* 971 (1958).
³⁸⁶ R. A. Nicolaus and G. Oriente, *Gazz. Chim. Ital.* **84**, 230 (1954).
³⁸⁷ W. Otting and H. Kainer, *Chem. Ber.* **87**, 1205 (1954).
³⁸⁸ R. A. Nicolaus and L. Mangoni, *Gazz. Chim. Ital.* **85**, 1378 (1955).
³⁸⁹ M. Scrocco and R. A. Nicolaus, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **20**, 797 (1956); *Chem. Abstr.* **52**, 9769 (1953).
³⁹⁰ W. Otting, *Chem. Ber.* **89**, 1940 (1956).
³⁹¹ J. Derkosch and E. Rieger, *Monatsh. Chem.* **90**, 389 (1959).
³⁹² H. W. Thompson and R. L. J. Popplewell, *Z. Elektrochem.* **64**, 746 (1960).
³⁹³ R. Laslett, M.Sc. Thesis, University of Adelaide (1964).
³⁹⁴ J. P. Perchard, M. T. Forel, and M. L. Josien, *J. Chim. Phys.* **61**, 660 (1964).
³⁹⁵ C. A. Frenzel, D. W. Scott, and J. P. McCullough, *U.S. Bur. Mines, Rept. Invest.* 5658 (1960); *Chem. Abstr.* **55**, 2278 (1961).
³⁹⁶ R. A. Jones, T. Pojarlieva, and R. J. Head, *Tetrahedron* **24**, 2013 (1968).
^{396a} P. Mirone, *Ann. Chim. (Rome)* **46**, 39 (1956).
^{396b} R. Soda, *Bull. Chem. Soc. Japan* **30**, 499 (1957).
^{396c} M. Yamaguchi, *Bunseki Kagaku* **7**, 210 (1958); *Chem. Abstr.* **54**, 3051 (1960).
^{396d} R. D. Hill and G. D. Meakins, *J. Chem. Soc.* p. 760 (1958).
^{396e} Y. Kanaoka, Y. Ban, T. Oishi, O. Yonemitsu, M. Terashima, T. Kimura, and M. Nakagowa, *Chem. & Pharm. Bull. (Tokyo)* **8**, 294 (1960).

dipole moment changes during the vibrations, but the effective interaction between the pyrrole ring and the substituent is considerably less through the ring nitrogen atom than through the α - or β -carbon atoms. Consequently, the effect of substituents on the band intensities is less for the 1-substituted pyrroles than for the 2- or 3-substituted compounds. The absorption band near 1400 cm^{-1} for 1-substituted pyrroles is assigned to the vibrational mode ν_5 on the basis of its high intensity which suggests a large dipole change during the vibration. It has been suggested³⁷⁴ that there is probably mixing of the N-C (substituent) stretching vibration with this ring-vibrational mode, particularly in the case of the 1-acylpyrroles. Conjugation of the ring π electrons with the carbonyl group of the 1-substituent imparts a partial double-bond character in the N-C (substituent) bond. This is reflected in an increase in the N-C stretching frequency to $1382\text{--}1360\text{ cm}^{-1}$ from the normal frequency of $1284 \pm 4\text{ cm}^{-1}$ observed for 1-alkylpyrroles.³⁷⁴ From the discussion of the spectrum of pyrrole it will be appreciated that the frequency of the ring-breathing mode, ν_3 , is in considerable doubt. With the lower symmetry of the substituted pyrroles the vibration should be IR-active, but no correlation has been made with any degree of certainty. Kreutzberger and Kalter,³⁷⁵ in their study of the spectra of mono- and polysubstituted pyrroles, assigned the band in the $990\text{--}870\text{ cm}^{-1}$ region to the ring-breathing mode by analogy with the spectra of other aromatic systems. However, it is possible that this band is a combination band (it has been suggested that the band at 960 cm^{-1} in the IR spectrum of pyrrole is a harmonic of the NH out-of-plane deformation).¹⁰⁷ A rather tentative correlation of the band at $1133 \pm 3\text{ cm}^{-1}$ with the ring-breathing vibration has been made for 2-substituted pyrroles.³⁷³ The intensity of the band increases with the electron-withdrawing ability of the substituent and is missing or very weak for saturated substituents. The intensity of the band is lowered on *N*-deuteration and completely absent for the 1-methyl derivatives and it appears that, with this possible exception, no substituted pyrrole has an absorption band which can be conclusively attributed to the ring-breathing mode either near 1100 cm^{-1} or at any lower frequency.

The position and intensities of the CH deformation bands depend on the number, orientation, and electronic type of the substituents. Interaction between the CH in-plane deformation and the NH in-plane deformation vibration, which absorbs near 1140 cm^{-1} , does not permit a direct comparison with correspondingly substituted furans or

thiophenes. The NH out-of-plane deformation mode absorbs near 500 cm^{-1} . Consequently, any interaction between the NH and CH out-of-plane deformations is negligible. Absorption bands attributable to in-plane deformations of four adjacent CH atoms are found at 1069 ± 6 (170 ± 70)^{396f} and $1027 \pm 9\text{ cm}^{-1}$ (85 ± 50), the CH out-of-plane vibrations absorb at 926 ± 4 (80 ± 60) and $722 \pm 2\text{ cm}^{-1}$ (425 ± 50). The characteristic absorption pattern for three CH atoms is 1090 ± 30 (65 ± 20), 1056 ± 3 (120 ± 65 for electron-withdrawing substituents and 25 ± 10 for saturated substituents), and $892 \pm 7\text{ cm}^{-1}$ (20 ± 10). Pyrroles having two adjacent hydrogen atoms absorb at 1035 ± 4 (40 ± 10), 973 ± 6 (20 ± 10), and $754 \pm 4\text{ cm}^{-1}$ (240 ± 35), whereas two isolated hydrogens cause absorption at 1054 ± 3 (165 ± 35), 934 ± 2 (75 ± 35), and $771 \pm 8\text{ cm}^{-1}$ (230 ± 70). For pyrroles having no substituent on the nitrogen atom, interaction of the NH in-plane deformation mode with the CH in-plane vibrations, in general, increases the frequency of the CH vibrational modes by *ca.* 10 cm^{-1} , but the positions of the CH out-of-plane absorption bands remain unchanged from those observed for the corresponding 1-substituted pyrroles.

Although a systematic investigation of the ring vibrations of polysubstituted pyrroles^{376, 377} has, in general, been neglected, considerable interest has been shown in the effect that the substituents of such compounds have on the frequency of the NH stretching vibrational mode. Italian work^{172, 238, 378, 379} has shown that electron-withdrawing substituents, which conjugate strongly with the pyrrole ring, lower the NH stretching frequency. In 1959, Abraham *et al.*¹⁸⁹ showed that the NH stretching frequencies of *C*-methylpyrroles could be expressed as a linear function of the number of α - and β -substituents, the frequency of the absorption being given by the following equation

$$\nu_{\text{NH}} (\text{cm}^{-1}) = 3497 - 10n_{\alpha} + 2n_{\beta}$$

where n_{α} and n_{β} are the number of α - and β -methyl groups, respectively, and 3497 cm^{-1} is the NH stretching frequency for unsubstituted pyrrole. Thus, α -methyl groups *decrease* the NH stretching frequency by 10 cm^{-1} contrary to the shift expected from the hyperconjugative effect of the methyl group. This effect was noted earlier by Scrocco

^{396f} The band positions are given as arithmetic means and standard deviations calculated from available data and omitting those compounds where the band is present as a shoulder. Values enclosed in parentheses are extinction coefficients.

et al.^{238, 378} The β -methyl group gives the expected increase in the NH stretching frequency. It was shown¹⁸⁹ that the effect of each methyl group on the NH stretching frequency is independent of other methyl groups and is additive. Further investigation has now been extended to include other substituents.^{165, 166, 166a} The results given in Table

TABLE XVI
NH FREQUENCY SHIFTS FROM 3496 cm^{-1} FOR
SUBSTITUTED PYRROLES^a

Substituent	α	β
Methyl	-9 ^b	2
Phenyl	-12	-7
Ethoxycarbonyl		-13
Isomer I ^c	-14	
Isomer II	-31	
Acetyl	-45	-18
Benzoyl	-42	-18
Formyl ^d	-36	-18
Cyano ^e	-22	-12

^a The NH stretching frequency of pyrrole is taken as 3496 cm^{-1} as reported by Mirone and Lorenzelli³⁷⁹ and Fuson *et al.*¹⁰³ Jones and Moritz¹⁶⁵ gave 3495 cm^{-1} and Abraham *et al.*¹⁸⁹ gave 3497 cm^{-1} .

^b Modified from that given in Ref. 189 to yield the best agreement when used with other substituent constants.

^c See text.

^d Calculated from the data given by Mirone and Lorenzelli.³⁷⁹

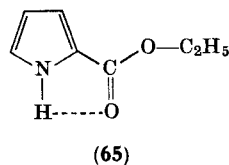
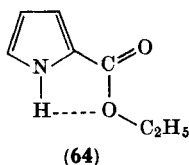
^e Unpublished results by R. A. Jones and L. F. Elsom.¹⁷⁷

XVI have shown that the effects of the individual substituents on the NH stretching frequency are additive and independent of the position and type of the other substituents and that the position of the absorption band may be represented by a single equation. For example, using the following equation and the constants given in Table XVI one would predict the NH stretching frequency of 3-ethoxycarbonyl-2-methyl-4,5-diphenylpyrrole to be 3455 cm^{-1} (the observed value is 3456 cm^{-1}).

$$\nu_{\text{NH}} (\text{cm}^{-1}) = 3496 - 9n_{\alpha}\text{CH}_3 - 13n_{\beta}\text{CO}_2\text{Et} - 12n_{\alpha}\text{Ph} - 7n_{\beta}\text{Ph}$$

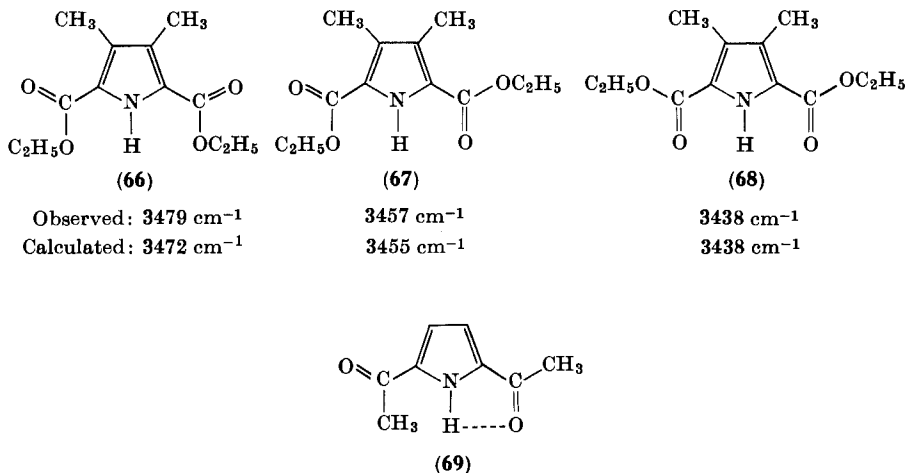
Miroshnichenko *et al.*³⁸⁰ have also shown that the frequency of the NH stretching vibration depends on the number of substituents and their electronegativity and that the effect is greater from the α -position than the β -position. However, it appears that under certain circumstances the substituent effects are not additive. Deviations of up to 7 cm^{-1} from the calculated value have been observed^{165, 166, 166a} when steric interaction between substituents do not allow them to exert their full conjugative effect.

During the course of these investigations it was found that for pyrroles having α -ester groups two concentration-independent bands, which could be attributed to the NH stretching mode, were observed.¹⁶⁵ These bands were assigned to the two rotational isomers (**64** and **65**), the lower frequency band being assigned to isomer (**65**). The comparatively small frequency shift of *ca.* 17 cm^{-1} between the



two isomers may arise from the stereochemistry involved, as the direction of the hydrogen bond would be approximately at 90° to the N-H axis. The similar intensities of the two bands imply that the two isomers are almost equally preferred and that the difference in hydrogen bond energies is small. Only one band was observed for α -acylpyrroles were the hydrogen-bonded structure, analogous to structure **65**, predominates to the exclusion of the nonbonded compound. This is in agreement with dipole moment measurements made by Marinangelli⁴⁷ for 2-acetylpyrrole. A notable disagreement between the calculated and observed frequencies arises when both the α - and α' -substituents are capable of hydrogen bonding with the NH group. For 2,5-diethoxycarbonyl-3,4-dimethylpyrrole three rotational isomers exist (**66**–**68**) and three absorption bands were observed. The deviations probably arise from changes in the strength of the hydrogen bond that lead to different frequency shift constants.

Discrepancies have also been reported¹⁶⁵ for 2-acetyl-5-ethoxycarbonyl-3,4-dimethylpyrrole, which shows two ν_{NH} absorption bands, and for 2,5-diacetylpyrrole, which exists predominantly as **69**⁴⁷ and shows only one band in the $3500\text{--}3400\text{ cm}^{-1}$ region.¹⁶⁶

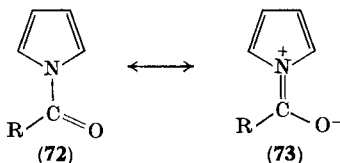
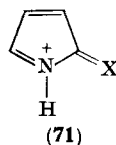
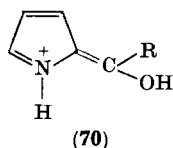


Two concentration-independent absorption bands, separated by *ca.* 20 cm⁻¹ and of relative intensity 20:1, have been observed^{165, 166, 166a} for 3-substituted pyrroles near 3500 cm⁻¹. The lower intensity band absorbing at the lower frequency has been assigned to the ν_{NH} "hot" band¹⁶⁵ (*cf.* Linnell³⁵²).

c. *Substituent Vibration Bands.* Most attention has been paid to the vibrational modes of electron-withdrawing substituents. The degree of conjugation of the substituent with the electron-donating ring has been measured in terms of the effect of the substituent on the NH-stretching frequency (*vide supra*) and the effect of the ring on the substituent vibrations.³⁸⁰ Mirone and his co-workers^{379, 381-383} have made a detailed study of pyrrole aldehydes. In concentrated solutions pyrrole-2-aldehydes are strongly associated (see Section II, B, 3), but in dilute solution in carbon tetrachloride the carbonyl-stretching frequency is observed near 1665 cm⁻¹ corresponding to the monomeric compound. The same vibrational mode absorbs at *ca.* 30 cm⁻¹ higher for pyrrole-3-aldehydes. This partly reflects the ability of the pyrrole nucleus to release electrons more readily through the 2-position than the 3-position, but also indicates the presence of intramolecular hydrogen bonding which lowers the frequency of $\nu_{\text{C=O}}$ for the 2-compound (*vide supra*). Alkyl groups tend to lower the frequency of the carbonyl-stretching mode, while further substitution of the ring by electron-withdrawing substituents produce an increase in the frequency. Bulky substituents on adjacent ring positions prevent

coplanarity of the formyl group with the ring, thereby reducing the degree of overlap of the π electrons. This is reflected in a higher C=O-stretching frequency.²⁶⁶ A similar pattern is observed for alkoxy-carbonyl^{165, 175, 231, 378, 384, 385} and acetyl pyrroles^{170-172, 174, 385} and for pyrrole carboxylic acids.^{238, 386-389} The C \equiv N-stretching frequencies for 3-cyanopyrroles are only slightly higher (*ca.* 8 cm⁻¹) than for 2-cyanopyrroles.^{177, 385} For these compounds intramolecular hydrogen bonding is impossible and the difference in frequencies is therefore directly related to the availability of electrons in the 2- and 3-positions.

The IR spectra of the conjugate acids of 2- and 3-acylpyrroles suggest that protonation occurs predominantly on the carbonyl oxygen atom^{206, 207} (see Section III, A, 1). This deduction appears to be based exclusively on the appearance of a strong band between 1630 and 1620 cm⁻¹ which was ascribed to the exocyclic C=C double bond (70). Strong absorption is also observed in the same region when there is particularly strong conjugation between the pyrrole ring and the



substituent and appears characteristic of resonance systems having a high contribution from the zwitterionic canonical form (71).

The C=O stretching frequency of 1-substituted pyrroles (72, R = alkyl, aryl, or alkoxy) is considerably higher than that of the corresponding 2- or 3-substituted compounds.^{166, 170, 205, 374, 390-393} Conjugation of the 1-substituent with the ring π electrons would be favored by the high π -electron density of the nitrogen atom and the zwitterionic canonical form (73) would be expected to contribute to the resonance structure. This is supported by the high intensity and frequency of the $>\dot{\text{N}}=\text{C}<$ stretching vibration. The conjugation effect

alone would be expected to give a $\nu_{C=O}$ frequency comparable with that of the 2- and 3-substituted compounds. The observed higher frequency results from the conflicting inductive effect of the nitrogen atom.

The spectra of alkyl^{346, 372, 394, 395} and aryl pyrroles^{374, 387} have been reported and the frequency and intensity of the C=C stretching modes of 2-(*trans-p*-substituted styryl)pyrroles has been used to study the long-range electronic interaction of the pyrrole ring with the *para* substituent.³⁹⁶

2. Electronic Spectra

Several investigators have measured the electronic spectrum of pyrrole and attempts have been made to include the data in a general interpretation on the spectra of the five-membered heteroaromatic systems, but no satisfactory correlation appears to have been reached. The vapor spectra of pyrrole³⁹⁷⁻⁴⁰⁰ and pyrrole-1-*d*^{397, 397a} show a series of broad and diffuse bands with some resolved vibrational structures extending through the ranges 220-190, 187-180, and 175-165 nm with maxima at 211, 183, and 172 nm, respectively, corresponding to transition energies of 5.88, 6.79, and 7.22 eV. A Rydberg series, which converges to give a value of the ionization potential of *ca.* 9.0 eV,^{398, 401} begins at 165 nm.³⁹⁹ A low-intensity band has also been reported extending over the region of 288-254 nm.³⁹⁹ The spectrum of pyrrole in hexane was originally reported⁴⁰² to have a band at 210 nm (ϵ 15,000), corresponding to the absorption between 220 and 190 nm observed in the vapor spectrum and also a less distinct band of considerably lower intensity near 240 nm ($\epsilon \sim 300$). These values were generally accepted, but they have recently been shown⁴⁰³ to be inaccurate and several deductions concerning the perturbing effects of substituents (*vide infra*) and, also, the classification of

³⁹⁷ G. Milazzo, *Spectrochim. Acta* **2**, 245 (1942).

^{397a} G. Milazzo, *Gazz. Chim. Ital.* **78**, 835 (1948).

³⁹⁸ W. Price and A. D. Walsh, *Proc. Roy. Soc. A* **179**, 201 (1941).

³⁹⁹ G. Milazzo, *Gazz. Chim. Ital.* **83**, 787 (1953).

⁴⁰⁰ L. W. Pickett, M. E. Corning, G. M. Wieder, D. A. Semenow, and J. M. Buckley, *J. Am. Chem. Soc.* **75**, 1618 (1953).

⁴⁰¹ cf. 8.97 ± 0.05 eV measured by H. Baba, I. Omura, and K. Higashi [*Bull. Chem. Soc. Japan* **29**, 521 (1956)] on a modified mass spectrometer and the calculated value of 9.03 by K. Maeda [*Bull. Chem. Soc. Japan* **31**, 890 (1958)].

⁴⁰² C. Menzel, *Z. Physik. Chem.* **125**, 161 (1927).

⁴⁰³ G. Horváth and Á. I. Kiss, *Spectrochim. Acta* **A23**, 921 (1967).

heteroaromatic systems by their electronic spectra⁴⁰⁴ have proved to be erroneous. It now appears that there is a closer correlation between the spectra of pyrrole and furan than with thiophene. The spectrum of a highly purified sample of pyrrole,⁴⁰³ measured in hexane, shows only one band at 207.5 nm (ϵ 7600), which has been ascribed to a singlet $\pi \rightarrow \pi^*$ transition.⁴⁰³ The long-wavelength bands which were originally reported are now attributed to impurities which may arise from an oxidation reaction. It has been shown that a distinct band appears in the solution spectrum of pyrrole at 296.5 nm when the solution is saturated with oxygen.^{404a, 407} As a result of the partial delocalization of the lone pair of electrons on the nitrogen atom into the π -electron system of the ring, the $n \rightarrow \pi^*$ transition band corresponding to the excitation of these electrons is not observed. Therefore (insofar as it is valid to treat the lone pair separately from the π system) the energy required to effect the $n \rightarrow \pi^*$ transition will be larger than that observed for six-membered aza aromatic systems and will most probably be hidden beneath the more intense $\pi \rightarrow \pi^*$ band.^{403, 408} The higher frequency absorption bands observed in the vapor spectrum are also attributed to singlet transitions,⁷³ but, to date, only limited agreement has been obtained between the experimental data and semiempirical theoretical calculations (see Section II,A). Theoretical calculations also suggest that the very weak absorption band which may be observed in the vapor spectrum near 285 nm and corresponds to a transition energy of 4.35 eV results from a singlet-triplet transition.⁷³

In spite of the proliferation of isolated UV spectral data for individual pyrroles, relatively few attempts have been made toward a systematic study of the effects of substituents upon the positions and intensities of the absorption bands. The detailed spectra of alkyl,^{192, 409} phenyl⁴¹⁰⁻⁴¹⁴ acyl,⁴¹⁵⁻⁴¹⁷ formyl,^{378, 418, 418a} and their oximino^{419, 420} and Schiff's base⁴²¹ derivatives, cyano,^{177, 378} car-

⁴⁰⁴ B. Ellis and P. J. F. Griffiths, *Spectrochim. Acta* **21**, 1881 (1965).

^{404a} This absorption band could be attributed to a charge-transfer complex,⁴⁰⁵ cf. the pyrrole-iodine complex.⁴⁰⁶

⁴⁰⁵ H. Tsubomura and R. S. Mullikan, *J. Am. Chem. Soc.* **82**, 5966 (1960).

⁴⁰⁶ R. P. Lang, *J. Am. Chem. Soc.* **84**, 4438 (1962).

⁴⁰⁷ D. F. Evans, *J. Chem. Soc.* 345 (1953).

⁴⁰⁸ S. F. Mason, *Phys. Methods Heterocyclic Chem.* **2**, 1 (1963).

⁴⁰⁹ G. V. Korshun and K. V. Rolla, *J. Russ. Phys.-Chem. Soc.* **55**, 253 (1924); *Chem. Abstr.* **19**, 2451 (1925).

boxamido,⁴²² halogeno-,²³⁷ nitro-,^{229, 378} 1-amino-,^{423, 424} and styryl-pyrroles^{396, 415} and pyrrolylcarboxylic acids^{238, 389} and esters^{378, 409, 410, 415, 422} have been reported and the data for selected compounds have been tabulated.^{6, 204, 425, 425a}

The introduction of methyl groups in place of hydrogen generally produces small bathochromic shifts (3–5 nm) of the pyrrole absorption maximum at 205 nm.^{192, 409} As a result of the early inaccurate determination of the absorption spectrum of pyrrole (*vide supra*), several investigators reached incorrect conclusions^{204, 425} concerning the perturbing effect of the alkyl substituents and it was originally reported that methyl groups always produced a hypsochromic shift with a lowering in the intensity of the absorption band. The intensity of the band actually decreases only with 1- and 3-substitution and increases on the introduction of a 2-methyl group,¹⁹² although even this generalization is not always true.²⁶⁶

The effects produced by other substituents on the position of absorption are, in general, similar to those observed within the benzene series. However, as a result of the inherent electron-donating

⁴¹⁰ G. V. Korshun and K. V. Rolla, *Bull. Soc. Chim. France* **43**, 1075 (1928).

⁴¹¹ B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.* **72**, 3379 (1950).

⁴¹² M. Fetizon, H. Fritel, J. Levisailles, and P. Baranger, *Compt. Rend.* **242**, 2014 (1956).

⁴¹³ S. M. King, C. R. Bauer, and E. Lutz, *J. Am. Chem. Soc.* **73**, 2253 (1951).

⁴¹⁴ R. W. Guy and R. A. Jones, *Australian J. Chem.* **19**, 1871 (1966).

⁴¹⁵ R. A. Jones and J. A. Lindner, *Australian J. Chem.* **18**, 876 (1965).

⁴¹⁶ G. V. Korshun and K. V. Rolla, *Trav. Inst. Chim., Kharkow* **1**, 9 (1935); *Chem. Abstr.* **32**, 4077 (1938).

⁴¹⁷ J. M. Patterson, J. Bausch, and P. Drenchko, *J. Org. Chem.* **26**, 4712 (1961).

⁴¹⁸ G. B. Bonino and A. Marinangelli, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **19**, 222 (1955); *Chem. Abstr.* **50**, 11111 (1956).

^{418a} G. B. Bonino and A. Marinangelli, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **19**, 393 (1955); *Chem. Abstr.* **50**, 12650 (1956).

⁴¹⁹ P. Ramart-Lucas, J. Hoch, and J. Klein, *Compt. Rend.* **232**, 336 (1951).

⁴²⁰ P. Ramart-Lucas, M. Grumez, J. Hoch, K. Klein, M. Martynoff, and M. Roch, *Bull. Soc. Chim. France* 1017 (1954).

⁴²¹ R. A. Jones, *Australian J. Chem.* **17**, 894 (1964).

⁴²² R. Andrisano, G. Pappalardo, and L. Bolognari, *Gazz. Chim. Ital.* **85**, 1430 (1955).

⁴²³ G. V. Korshun and K. V. Rolla, *Bull. Soc. Chim. France* **37**, 130 (1925).

⁴²⁴ G. V. Korshun and K. V. Rolla, *Bull. Soc. Chim. France* **39**, 1223 (1926).

⁴²⁵ U. Eisner and P. H. Gore, *J. Chem. Soc.* 922 (1958).

^{425a} Absorption bands ascribed to the conjugate acids of the acyl, alkoxy-carbonyl, and nitro pyrroles in Schofield,⁶ (pp. 55–56) actually refer to the free base.

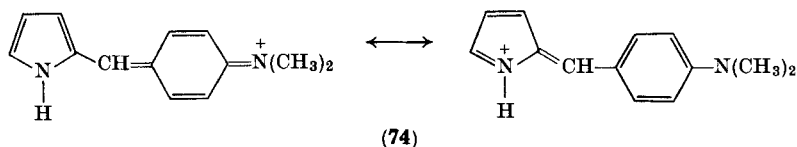
effect of the pyrrole ring, the bathochromic shifts observed upon the introduction of electron-withdrawing substituents are considerably larger than for the corresponding phenyl compound (Table XVII). In

TABLE XVII

THE EFFECT OF CONJUGATION ON THE LONG WAVELENGTH ABSORPTION BAND OF α -SUBSTITUTED PYRROLES AND MONOSUBSTITUTED BENZENES

Substituent	Pyrrolyl compound				Phenyl compound			
	nm	ϵ	nm	ϵ	nm	ϵ	nm	ϵ
COMe	250	4,400	287	15,900	—	—	243	13,200
<i>trans</i> -CH=CHCOMe	269	1,700	353	23,300	—	—	285	22,400
Ph	230	8,000	287	20,300	—	—	252	18,300
<i>trans</i> -CH=CH·Ph	236	8,400	330	27,800	228.5	16,200	294	27,900
	—	—	342	8,000	—	—	—	—

the pyrrole series, the introduction of a carbonyl group produces a bathochromic shift of *ca.* 30–50 nm with the appearance of a second intense absorption band in the region 260–300 nm. The position of this new long-wavelength band moves to longer wavelengths with the increasing conjugative power of the substituent (Table XVII). Extremely strong electron-withdrawing substituents shift the long wavelength band into the visible region, as, for example, is the case of the condensation products obtained from the Ehrlich reagent and an α -unsubstituted pyrrole (74) in which the long-wavelength absorption is observed near 525 and 560 nm.^{426, 427}



For all 3-substituted pyrroles the long-wavelength absorption is usually 15–20 nm lower than for the corresponding 2-derivatives, indicating that although the difference in conjugation energy in the

⁴²⁶ P. Formijne and N. J. Poulie, *Koninkl. Ned. Akad. Wetenschap., Proc.* **C57**, 57 (1954).

⁴²⁷ M. A. Muhs and F. T. Weiss, *Anal. Chem.* **30**, 259 (1958).

ground state for the 2- and 3-isomers is of the order of 2.5–3.0 kcal/mole,^{428, 429} the conjugation in the excited state is considerably more pronounced for the 2-substituted compounds. The difference in conjugation energy in the excited state for 2- and 3-substituted compounds has been estimated to be of the order of 6 kcal/mole.⁴²⁵ In contrast with the correspondingly substituted benzene compounds, the intensity of the long-wavelength absorption for substituted pyrroles is governed largely by the position of the substituent rather than by the electronic type of the substituent. Thus the absorption band for the 3-substituted compounds invariably has a considerably lower intensity ($\epsilon < 7500$) than the corresponding band for the 2-substituted compounds ($\epsilon > 12,000$) (see, e.g., Elsom¹⁷⁷ and Eisner and Gore⁴²⁵).

The occurrence of $d_{\pi}-p_{\pi}$ bonding involving overlap of the π orbital of the electron-donating pyrrole ring with the phosphorus d -orbital in tri-2-pyrrolylphosphine oxide has been established by the observation of a band at 237.5 nm (ϵ 11,480).^{430, 431} Such a large bathochromic shift, together with the high intensity of the absorption, which is comparable with that observed for pyrrole esters, cannot be rationalized in terms of any inductive effect, but is indicative of a mesomeric conjugative interaction.

The general appearance of the spectra of 1-substituted pyrroles is similar to that of pyrrole.^{432, 433} *N*-Alkyl substituents produce a shift of ca. 5–10 nm of the pyrrole absorption maximum at 205 nm towards the red with little change in intensity, but substitution of an acyl group in the 1-position produces an increase in intensity together with a bathochromic shift of ca. 35 nm and the appearance of a band at 288 nm (ϵ 760). It has been suggested⁴³⁴ that this new weak absorption band probably results from an $n \rightarrow \pi^*$ transition rather than from conjugation of the substituent with the ring.

The spectra of conjugate acids of pyrrole and of pyrrolyl anions have also been investigated (see Section III, A, 1). Protonation of the

⁴²⁸ A. Stern and G. Klebs, *Ann. Chem.* **500**, 107 (1932).

⁴²⁹ A. Stern and G. Klebs, *Ann. Chem.* **504**, 296 (1933).

⁴³⁰ C. E. Griffin and R. A. Polsky, *J. Org. Chem.* **26**, 4772 (1961).

⁴³¹ C. E. Griffin, R. P. Peller, K. R. Martin, and J. A. Peters, *J. Org. Chem.* **30**, 97 (1965).

⁴³² G. Milazzo and E. Miescher, *Gazz. Chim. Ital.* **83**, 782 (1953).

⁴³³ G. Milazzo and E. Miescher, *J. Phys. Radium* **15**, 401 (1954).

⁴³⁴ H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy." Wiley, New York, 1962.

pyrrole ring produces a bathochromic shift of the absorption band of the pyrrole ring without any large change in intensity.¹⁹² The absorption maxima for α -protonated pyrroles lie near 245 nm, whereas β -protonation shifts the band to *ca.* 270 nm.¹⁹² Protonation of pyrroles having electron-withdrawing substituents most probably occurs upon the substituent and no generalization can be made as to the effect of protonation on the electronic absorption spectra.¹⁸⁷

3. NMR Spectra

a. *Proton Magnetic Resonance.* The PMR spectrum of pyrrole consists of a very broad line at low field attributable to the proton of the NH group and a complex eight-line multiplet attributable to the ring protons (Fig. 5a).^{119, 122, 134, 139, 435-437} Exchange of the NH proton by deuterium simplifies the CH signals into two triplets¹³⁴ (Fig. 5b) and the chemical shift difference between the triplets increases in solution spectra.¹³⁴ Similarly, the eight-line multiplet of pyrrole separates into two distinct quartets in dilute solution^{119, 134} (Fig. 5c).

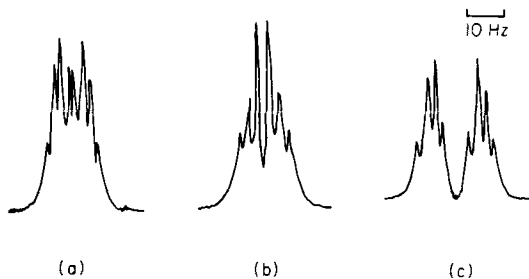


FIG. 5. Nuclear magnetic resonance signals of the pyrrole ring protons. (a) Pure liquid pyrrole, (b) pure liquid pyrrole-1-*d*, and (c) dilute solution of pyrrole in CCl_4 .

In deuteriochloroform the resonances appear at τ 3.32 and 3.78.⁴³⁵ These spectra have been interpreted¹³⁴ in terms of the α -protons giving the low field signals and the β -protons the higher field signals. The triplet splitting of the signals for pyrrole-1-*d* suggests that the spin-coupling of adjacent protons $J_{\alpha\beta}$, is equal to the coupling across the

⁴³⁵ "Varian N.M.R. Spectra Catalog," Vol. 1, Spectrum 55. Varian Associates, Palo Alto, California, 1962.

⁴³⁶ B. Dischler and G. Englert, *Z. Naturforsch.* **16a**, 1180 (1961).

⁴³⁷ B. Dischler, *Z. Naturforsch.* **20a**, 888 (1965).

ring, $J_{\alpha\beta}$. A subsequent detailed analysis^{263, 264} of the spectra of substituted pyrroles, however, indicated that the two coupling constants, although almost identical, differ slightly and that the observed splitting of the triplets was an averaged value of $J_{\alpha\beta}$ and $J_{\alpha\beta'}$.^{134, 438} As it is reasonable to assume that the coupling constants for pyrrole are identical to those of pyrrole-1-*d*, the quartets observed in the spectrum of pyrrole must arise from further coupling of the α - and β -proton with the imino proton. The quartet character suggests that $J_{\alpha\text{-NH}}$ and $J_{\beta\text{-NH}}$ are equal, but here again this is highly improbable and it is most likely that average coupling constants are observed. The broad signal from the imino proton results from the rapid electric quadrupolar relaxation of the ^{14}N nucleus which partially decouples the nitrogen-hydrogen coupling and thus causes the lines to be broadened.⁴³⁹ Double irradiation at the ^{14}N resonance frequency of 2.9 MHz sharpens the signal to give a five-line multiplet arising from coupling of the imino proton with the α - and β -protons.¹¹⁹ This is contrary to the report of a broad triplet under similar decoupling conditions.^{439, 440} The α - and β -protons remain as distinct quartets.

From observations^{263, 264} of the PMR spectra of several substituted pyrroles, in which the NH proton had been decoupled from the ring protons, the coupling constants of the ring protons appear to fall into four distinct ranges: $J_{\beta\beta'} = 3.40\text{--}3.80$, $J_{\alpha\beta} = 2.40\text{--}3.10$, $J_{\alpha\beta'} = 1.95\text{--}2.20$, and $J_{\alpha\beta} = 1.35\text{--}1.50$ Hz. The $J_{\alpha\text{-NH}}$ and $J_{\beta\text{-NH}}$ coupling constants have been shown²⁶³ to lie in the range 2.20–2.70 Hz. Use has been made of these characteristic values of the coupling constants as an aid to the elucidation of the structure of substituted pyrroles.^{441, 442} An analysis of the spectrum of pyrrole in terms of an $\text{A}_2\text{B}_2\text{X}$ system⁴³⁶ has been reported, which, by making use of information from ^{13}C satellite bands, has provided an improved set of spin-coupling parameters: $J_{\alpha\beta} = 2.1$, $J_{\beta\beta'} = 3.7$, $J_{\alpha\beta} = 2.7$, $J_{\alpha\beta'} = 1.3$, $J_{\alpha\text{-NH}} = 2.6$, $J_{\beta\text{-NH}} = 2.3$ Hz. Attempts to explain the magnitudes of the cross ring-coupling

⁴³⁸ R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **39**, 216 (1961).

⁴³⁹ J. D. Roberts, *J. Am. Chem. Soc.* **78**, 4495 (1956).

⁴⁴⁰ J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, p. 457. Pergamon Press, Oxford 1965.

⁴⁴¹ S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom, and R. A. Hoffmann, *Arkiv Kemi* **18**, 151 (1961).

⁴⁴² S. Gronowitz, A.-B. Hörnfeldt, and B. Gestblom, *J. Org. Chem.* **26**, 2615 (1961).

constants, $J_{\alpha\beta'}$ and $J_{\alpha\alpha'}$, in terms of the hybridization of the nitrogen atom have been made.⁴⁴³ Whereas the value of $J_{\alpha\beta}$ depends largely on the heteroatom and is roughly the same for furan and pyrrole, but considerably larger for thiophene, the size of $J_{\beta\beta'}$, which is further removed from the influence of the heteroatom, is approximately constant at between 3.0 to 4.0 Hz for all three rings. Thus for furan and pyrrole $J_{\beta\beta'}$ is always larger than $J_{\alpha\beta}$, but for thiophene the reverse is true.⁴⁴³ Spin-decoupling experiments⁴⁴⁴ on the sodium salt of pyrrole-2-carboxylic acid indicated that the $J_{\alpha\beta}$, $J_{\alpha\beta'}$, and $J_{\beta\beta'}$ coupling constants have the same sign and it has been assumed that, by analogy with thiophene and furan, the sign of $J_{\alpha\alpha'}$ will be the same.

It is generally accepted that the π -electron system of the pyrrole nucleus is capable of sustaining an induced ring current which contributes significantly to the chemical shifts of the ring protons and substituents. The magnitude of the effect bears a direct relationship to the aromaticity of the ring, but, because of the difficulty in selecting a suitable nonaromatic standard for comparison,^{74, 445-447} the significance of the reported degree of aromatic character for five-membered heterocyclics has been criticized. Elvidge⁴⁴⁵ studied the chemical shift data for 2-methylpyrrole and, using a linear polyene and *sec*-butylamine as his nonaromatic standards, he calculated a ring current shift of 0.21 ppm which is equivalent to an aromaticity of 0.59 compared with 1.00 for benzene. This value agrees well with that derived from experimental resonance energies (see Section II, A). The effect of substituents on the nitrogen atom upon the aromaticity of the pyrrole ring has been investigated for a series of 1-substituted-pyrroles, -2,5-dimethylpyrroles, and -3,4-dimethylpyrroles.²⁶¹ The variations in the chemical shifts of both the pyrrole ring proton and methyl resonances with a change in the 1-substituent present no evidence for any appreciable variation in the pyrrole ring current. It was suggested that for 1-arylpyrroles the interaction between the rings was essentially an inductive effect, and, although it did not produce any significant change in the ring current within the

⁴⁴³ R. A. Hoffmann and S. Gronowitz, *Arkiv Kemi* **16**, 563 (1961).

⁴⁴⁴ A. D. Cohen and K. A. McLaughlan, *Discussions Faraday Soc.* **34**, 132 (1962).

⁴⁴⁵ J. A. Elvidge, *Chem. Commun.* 160 (1965).

⁴⁴⁶ R. J. Abraham, R. C. Sheppard, W. A. Thomas, and S. Turner, *Chem. Commun.* 43 (1965).

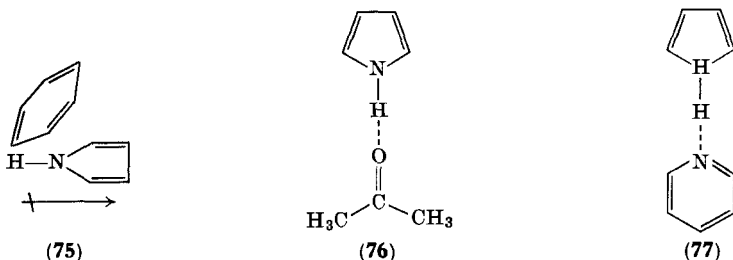
⁴⁴⁷ P. J. Black, R. D. Brown, and M. L. Heffernan, *Australian J. Chem.* **20**, 1305 (1967).

pyrrole ring, the reactivity of the pyrrole ring may well be affected by variations in the electron densities as a result of the inductive interaction.

Solvent-induced shifts^{119, 127, 134-136, 139, 140, 142, 148, 151, 152, 164} of the proton resonances can result from two different effects. Dissolution of pyrrole in a nonpolar and nonaromatic solvent causes disruption of the self-association of the pyrrole molecules (see Section II, B) which results in the chemical shift of the α -protons moving to significantly lower fields on dilution, while the signal for the β -protons shifts only slightly downfield^{119, 122, 139} (Fig. 5c). The NH proton resonance also moves to lower field on dilution of the solution.¹¹⁹ This is consistent with self-association of the pyrrole molecules via NH- π interactions (see Section II, B, 1, a). The solvent-induced shifts caused by non-hydrogen-bonding polar solvents result from specific solvation of the pyrrole ring by a dipole-dipole or π -dipole interaction, whereas polar solvents capable of hydrogen bonding solvate either via interaction with the π electrons of the pyrrole ring, where the solvent is a proton donor as, for example, with chloroform,¹⁴² or alternatively the solvent acts as a proton acceptor, as is the case with pyridine,¹¹⁹ and forms a hydrogen bond with the NH group. Thus, it is thought that benzene solvates by a π -dipole interaction (75), producing a characteristic upfield shift in the α -proton resonances relative to the measurements made in carbon tetrachloride of up to 0.3 ppm and a corresponding downfield shift of the β -proton of between 0.3 to 0.6 ppm.¹⁵¹ That the interaction is not NH- π hydrogen bonding is apparent from the observations that *N*-alkylation produces increased negative shifts of the β -protons.^{151, 448} This is in accord with the increased dipole moment of 1-methylpyrrole.²⁵² The dipole moment of pyrrole in benzene is best rationalized in terms of NH- π bonding in an orthogonal configuration (Section II, B, 1, b) and this is strongly supported by the sign of the solvent dependence of the Kerr constant.¹⁵⁵ It has been suggested, however, that to account for the magnetic shielding of the α - and β -protons of pyrrole in benzene solution it requires the presence of a second molecule of benzene oriented at about 35° to the pyrrole ring.¹⁵⁵ *C*-Methyl group resonances shift in a corresponding manner to the ring proton resonances, but the shielding of the *N*-methyl group by the benzene ring induces upfield shifts of up to 0.7 ppm.¹⁵¹ Other types of solvation do not affect the chemical shift of the

⁴⁴⁸ J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.* **43**, 1849 (1965).

N-methyl group to such a large extent.⁴⁴⁸ Similarly, solvents such as acetone may solvate either via dipole-dipole interactions, or alternatively, by hydrogen bonding with the NH group. It has been



assumed,^{139, 149} and probably correctly so, that the solvation of pyrrole by acetone involves hydrogen bonding (76). The α -proton resonances are concentration dependent and shift to low field, whereas the β -proton resonances are relatively unaffected. That this effect may not entirely result from hydrogen-bonded solvation is evident from the PMR spectrum of *N*-butylpyrrole,¹³⁹ in which solvent-induced shifts of a similar nature are observed, and yet for which only a dipole-dipole interaction can be envisaged. An alternative, but somewhat less likely explanation has been postulated which interprets the observation in terms of preferential hydrogen bonding of the acetone with the α -protons of the pyrrole ring.¹³⁹ The PMR spectrum of pyrrole in acetone⁴³⁶ has been reported to change considerably at high temperatures and that the α - and β -proton resonances appear as triplets with effectively no coupling between the imino proton and the α - and β -protons. Amines and azines solvate pyrroles specifically by NH-N hydrogen bonding (77).¹¹⁹ The position of the NH resonance is strongly dependent upon the concentration of pyridine and shifts to lower fields. This should be compared with the effect of proton-acceptor concentration on the induced solvent shifts from NH- π interactions (*vide supra*). Use of this solvent shift of the NH resonance has been made to calculate the stability constant for the pyrrole-pyridine complex (77).¹¹⁹ Sufficiently strong bases, for example, piperidine,⁴³⁷ promote rapid exchange of the imino proton and consequently remove the coupling between the imino proton and the ring protons. Dimethyl formamide²⁶⁴ and dimethyl sulfoxide¹⁵³ have also been used for this purpose. The addition of potassium^{189, 449} or

⁴⁴⁹ N. Joop and H. Zimmermann, *Z. Elektrochem.* **66**, 440 (1962).

sodium²⁶⁴ to pyrrole has been shown to decouple the imino proton by the rapid exchange of the proton between pyrrole and the pyrrolyl anion. The α - and β -proton resonances were observed as triplets at τ 4.00 and 4.18 and the NH resonance at τ 3.04 increased in intensity and sharpness as the concentration of the anion in the pyrrole was increased.

Detailed analyses of both the chemical shifts and the coupling constants have been reported for a number of substituted pyrroles^{134, 189, 192, 261, 263, 264, 438, 441, 442, 450, 451} and the pyrrolyl anion.²²⁷ The structures of many compounds have been verified by the use of one or the other of these parameters (see, e.g.,^{54, 237, 441, 442, 452, 453}). Of particular interest is a study of the structure of the pyrrole Grignard reagent.²²⁷ The site of protonation of the pyrrole ring by acids has also been investigated and the basicities of several pyrroles determined using PMR spectroscopy¹⁸⁹⁻¹⁹³ (see Section III, A, 1).

Substitution of a methyl group in place of a proton in an unsubstituted pyrrole ring produces a redistribution of the π -electron density and, in general, causes an upfield shift of the resonances of the remaining ring protons.^{189, 450} The total effect on the chemical shifts of the ring protons by the introduction of one methyl group has been shown to be of the order of 0.73 ppm. For 2-methylpyrrole the chemical shifts of the 3-, 4-, and 5-protons were 0.39, 0.17, and 0.17 ppm, respectively, upfield from the α - and β -proton resonances of pyrrole. These values are very similar to those of 2-methylfuran, but differ from those of 2-methylthiophene, the proton resonances of which are affected almost to the same extent in all three positions. This has been taken as being indicative of the higher aromatic character of the thiophene and substantiates the evidence obtained from a consideration of the "ring current shift" and spin-coupling constants (*vide supra*).

The spin-coupling of ring protons has been used in studies of the conformation of acyl pyrroles.^{262, 266, 454} Restricted rotation about the N-C(O) bond of 1-mesitylpyrrole has been shown to be less at high

⁴⁵⁰ G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.* **83**, 5020 (1961).

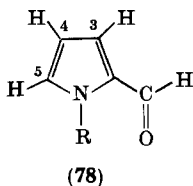
⁴⁵¹ R. M. Acheson, *J. Chem. Soc.* 2630 (1965).

⁴⁵² J. H. Atkinson, R. S. Atkinson, and A. W. Johnson, *J. Chem. Soc.* 5999 (1964).

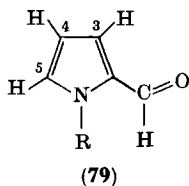
⁴⁵³ H. J. Anderson and L. C. Hopkins, *Can. J. Chem.* **44**, 1831 (1966).

⁴⁵⁴ A. Mannshreck, H. A. Staab, and D. Wurmb-Gerlich, *Tetrahedron Letters* 2003 (1963).

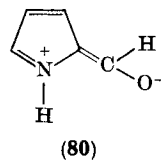
temperatures.^{454, 454a} The evidence from IR spectral data¹⁶⁶ and dipole moment studies⁴⁷ that 2-formylpyrrole exists predominantly in conformation **78** (R = H) and not **79** (R = H) is strongly supported by PMR measurements.²⁶² Partial double-bond character of the (ring) C-C(O) bond (**80**) would restrict rotation and intramolecular hydrogen bonding between the carbonyl group and the imino proton,¹⁶⁶ although weak, would tend to stabilize conformation (**78**, R = H). The resonance signal of the formyl proton of 2-formylpyrrole is a doublet at room temperature²⁶²⁻²⁶⁶ with a coupling constant of 1.2 Hz and evidence²⁶⁴ has been provided to show that this proton is coupled through the heteroatom with the proton in the 5-position. The apparent absence of any coupling of the formyl proton with the 4-hydrogen, together with an application of the "straightest zigzag coupling path" rule⁴⁵⁵ precludes conformation **79**.^{263, 266} The formyl proton of the 1-alkyl-2-formylpyrroles is also



$$\begin{array}{ll} J_{\text{CHO}-5\text{H}} & 1 \text{ Hz} \\ J_{\text{CHO}-4\text{H}} & 0 \text{ Hz} \end{array}$$



$$\begin{array}{ll} J_{\text{CHO}-5\text{H}} & 0 \text{ Hz} \\ J_{\text{CHO}-4\text{H}} & 0.8 \text{ Hz} \end{array}$$



coupled with the 5-hydrogen.²⁶⁶ Thus, in spite of steric hindrance between the carbonyl group and the *N*-alkyl group, these compounds exist in conformation **78** (R = alkyl). The major factor controlling the conformation appears to be the interaction of the carbonyl dipole with the ring π dipole. The existence of 1-*t*-butyl-2-formylpyrrole in conformation **78** can readily be rationalized in terms of these interactions, as can the predominance at room temperature of conformation **79** (R = CO₂Et) for 1-ethoxycarbonyl-2-formylpyrrole.⁴⁵⁶ Anomalous coupling has been reported between the formyl proton and

^{454a} See also the recent investigation of the restricted rotation about the CN bond of 1-formyl, 1-acetyl, and 1-benzoylpyrrole [T. Matsuo and H. Shosenji, *Chem. Commun.* 501 (1969)].

⁴⁵⁵ C. N. Banwell and N. Sheppard, *Discussions Faraday Soc.* **34**, 115 (1962).

⁴⁵⁶ R. A. Jones and P. H. Wright, unpublished work (1967).

the ring hydrogens for furfural,^{457, 457a} but there is little justification for extending these results to the formyl pyrroles.

Long-range coupling has also been observed in other pyrrole compounds.^{134, 458-460}

b. ¹³C and ¹⁴N Magnetic Resonance. The major interest involving ¹³C nuclear magnetic resonance has been mainly the correlations of ¹³C-H spin-coupling constants⁴⁶¹⁻⁴⁶⁴ and, to a lesser extent, ¹³C chemical shifts^{78, 463, 464} with the hybridization of the carbon atoms and the aromaticity of the pyrrole ring. The ¹³C-H spin-coupling constants for pyrrole have been found^{461, 462, 464} to be in the range 182 to 184 Hz for α -¹³C-H and in the range 169.8 to 171 Hz for β -¹³C-H, with little variation from these values for either C- or N-methyl derivatives.⁴⁶¹⁻⁴⁶⁴ The ¹³C-H coupling constants for C-methyl substituents are of the order of 127 to 128 Hz^{463, 464} and are slightly larger, 137 to 139.5 Hz, for N-methyl groups.^{461, 463} The ¹³C chemical shifts for pyrrole, its anion, and several methyl-substituted pyrroles have been measured and some attempts have been made to estimate electron densities and the size of the aromatic ring current.^{78, 463, 464}

Due, in the main, to quadrupolar line-broadening effects, together with the poor sensitivity, there has been relatively little general interest in ¹⁴N magnetic resonance studies and, although the quadrupolar broadening has been shown to be minimized by the use of low viscosity solvents,⁴⁶⁵ the ¹⁴N chemical shifts of only four pyrroles have been reported.^{465, 466} The ¹⁴N chemical shift of pyrrole has been reported as either 230⁴⁶⁵ or 227⁴⁶⁶ ppm relative to the NO₂⁻ ion ¹⁴N resonance, and values of 227, 230, and 225 ppm have been recorded for 1-methylpyrrole, 2,5-dimethylpyrrole, and 1-methyl-2-methoxycarbonylpyrrole, respectively.⁴⁶⁵ The associated effect of electric

⁴⁵⁷ K. I. Dahlqvist and S. Forsen, *J. Phys. Chem.* **69**, 1760 (1965).

^{457a} K. I. Dahlqvist and S. Forsen, *J. Phys. Chem.* **69**, 4062 (1965).

⁴⁵⁸ R. J. Tuite, A. D. Josey, and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 4360 (1960).

⁴⁵⁹ H. S. Gutowsky and A. L. Porte, *J. Chem. Phys.* **35**, 839 (1961).

⁴⁶⁰ R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.* **65**, 187 (1961).

⁴⁶¹ K. Tori and T. Nakagawa, *J. Phys. Chem.* **68**, 3163 (1964).

⁴⁶² B. Dischler, *Z. Naturforsch.* **19a**, 887 (1964).

⁴⁶³ J. H. Goldstein and G. S. Reddy, *J. Chem. Phys.* **36**, 2644 (1962).

⁴⁶⁴ T. F. Page, T. Alger, and D. M. Grant, *J. Am. Chem. Soc.* **87**, 5333 (1965).

⁴⁶⁵ D. Herbison-Evans and R. E. Richards, *Mol. Phys.* **8**, 19 (1964).

⁴⁶⁶ M. Bose, N. Das, and N. Chatterjee, *J. Mol. Spectry.* **18**, 32 (1965).

quadrupolar relaxation of the ^{14}N nucleus on the coupling of the imino hydrogen with the nitrogen atom has been studied in detail.^{119, 439} A value of $J_{14\text{N-H}}$ of 69.5 ± 1 Hz has been reported⁴⁶⁷ for pyrrole and its 2,3,4,5-tetradeutero derivative.

⁴⁶⁷ E. Rahkama, *J. Chem. Phys.* **48**, 531 (1968).

Quinuclidine Chemistry¹

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I. Introduction

Quinuclidine (1-azabicyclo[2.2.2]octane) is a heterocyclic system which is part of the structure of a number of natural physiologically active compounds and synthetic drugs.^{1a} Among the natural alkaloids, the following quinoline and indole derivatives contain the quinuclidine ring: cinchonine, cinchonamine (alkaloids of *Cinchona* species),⁸⁻¹²

¹ To the memory of my teacher and friend Professor Mikhail Vasil'evich Rubtsov.

^{1a} Some reviews describing the development of quinuclidine chemistry have been published.^{1b-7}

^{1b} M. V. Rubtsov, E. E. Mikhлина, and L. N. Yakhontov, *Usp. Khim.* **29**, 74 (1960).

² W. L. Mosby, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 15, p. 1331. Wiley (Interscience), New York, 1961.

³ G. Ing, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 3, p. 361. Wiley, New York, 1952.

⁴ M. V. Rubtsov and L. N. Yakhontov, "Osnovnye Napravleniya Rabot Vses. Nauch.-Issled. Khim.-Farmatsevt. Inst. 1920-1957" pp. 281-300. Moscow. 1959; *Chem. Abstr.* **55**, 25978 (1961).

⁵ L. N. Yakhontov, *Acta Polon. Pharm.* No. 1, 1 (1958).

⁶ M. V. Rubtsov and L. N. Yakhontov, *Česk. Farm.* **7**, 520 (1958).

⁷ G. R. Clemons, *J. Chem. Soc.* 2057 (1955).

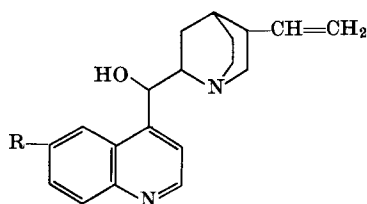
⁸ H. G. Boit, "Ergebnisse der Alkaloid-chemie bis 1960," pp. 563 and 572. Akademie Verlag, Berlin, 1961.

⁹ R. Manske, "The Alkaloids." Academic Press, New York, 1953.

¹⁰ T. A. Henry, "The Plant Alkaloids." Churchill, London, 1949.

sarpagine, ajmaline (*Rauwolfia* alkaloids),^{8, 13, 14} and makusine (*Strychnos* alkaloids)^{15, 16}

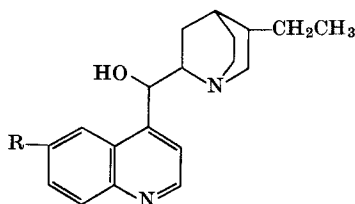
Cinchonine and cinchonamine alkaloids:



R = H Cinchonine, cinchonidine

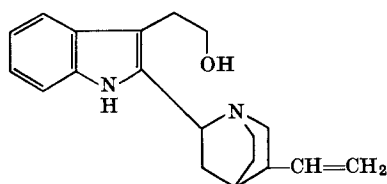
R = OH Cupreine

R = OCH₃ Quinine, quinidine,
epiquinine, epiquinidine

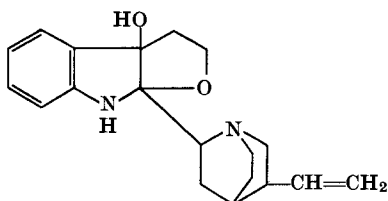


R = H Hydrocinchonine,
hydrocinchonidine

R = OCH₃ Hydroquinine,
hydroquinidine



Cinchonamine



Quinamine, conquinamine

¹¹ A. P. Orekhov, "Khimiya Alkaloidov" (The Chemistry of Alkaloids), 2nd ed. Izd. Akad. Nauk S.S.S.R., Moscow, 1955.

¹² N. A. Preobrazhenskii and E. I. Genkin, "Khimiya Organicheskikh Lekarstvennykh Veshchestv" (The Chemistry of Organic Medicinal Compounds). Goskhimizdat, Moscow, 1953.

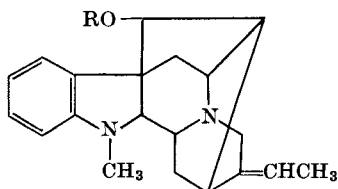
¹³ L. N. Yakhontov, *Usp. Khim.* **26**, 239 (1957).

¹⁴ R. E. Woodson, H. W. Joungken, E. Schlittler, and J. A. Schneider, "Rauwolfia." Little, Brown, Boston, Massachusetts, 1957.

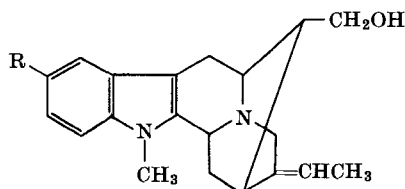
¹⁵ A. R. Battersby and D. A. Jeowell, *J. Chem. Soc.* 4419 (1954).

¹⁶ G. V. Binst, J. C. Nouis, J. Stokol, C. Danheux, and R. H. Martin, *Bull. Soc. Chim. Belges* **74**, 506 (1955).

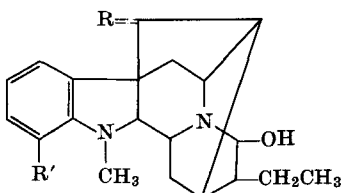
Sarpagine, ajmaline, and makusine alkaloids:



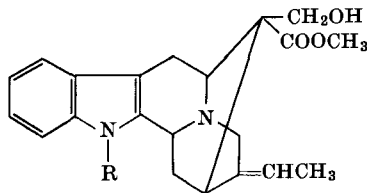
R = H Tetraphyllicine

R = $(\text{CH}_3\text{O})_3\text{C}_6\text{H}_2\text{CO}$ Sauvomitine

R = OH Sarpagine

R = OCH₃ LochnerineR = OH + H, R' = H Ajmaline,
isoajmaline,
sandvicine

R = O, R' = H Ajmalidine

R = O, R' = OCH₃ Vomalidine

R = H Makusine A

R = CH₃ Voachalotine

In view of the high chemotherapeutic activity of *Cinchona* alkaloids, of which quinine is the most important as an antimalarial medicine, scientists of many countries have spent much time investigating syntheses of quinine and its analogs.

The increase in heart muscle excitability induced by some natural quinuclidine derivatives (quinidine, ajmaline), suggesting pharmacological activity of some synthetic quinuclidine compounds and the possibility of using quinuclidines as catalysts for production of polymers,¹⁷ stimulated further interest in the ring system.

The total synthesis of quinine by Woodward and Doering¹⁸ in 1944 and synthesis of cinchonamine made in 1958 by Chen *et al.*¹⁹ are among the main achievements in research on the natural quinuclidine

¹⁷ H. J. Twitchett and E. J. Vickers, British Patent 889,048 (1962); *Chem. Abstr.* **57**, 2422 (1962).

¹⁸ R. B. Woodward and W. E. Doering, *J. Am. Chem. Soc.* **67**, 860 (1945).

¹⁹ Chen Chang By, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Dokl. Akad. Nauk SSSR* **123**, 707 (1958).

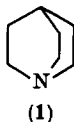
compounds. The total synthesis of racemic homomeroquinene was carried out by Rubtsov²⁰ starting from trichlorocollidine.

There are several specialized reviews^{8-12,21} pertaining to the natural quinuclidine derivatives, in particular to the history of their discovery, practical uses, natural sources, methods of analysis, extraction and isolation, and structural determination, as well as their stereochemistry and chemical reactions. Such material is therefore excluded from this chapter.

The main attention of the present review is concentrated on the general chemical properties and peculiarities of quinuclidine derivatives, methods for building up quinuclidine systems (methods for quinuclidine ring closure), methods for substituent introduction in quinuclidine molecules, and biological properties of quinuclidine derivatives.

II. Some Features of Quinuclidine Derivatives

Quinuclidine (1) is a saturated bicyclic system with a bridgehead nitrogen atom. It has, in contrast to tertiary aliphatic amines and *N*-substituted piperidines, a rigid structure. The atoms forming the quinuclidine ring are incapable of changing their relative positions by rotation around bond axes. These bond axes are included in the bicyclic system with each ring in the boat form.



In contrast to other 1-azabicycloalkanes, quinuclidine is notable for its high symmetry and for the insignificant bond strain. The nitrogen lone-pair electrons are sp^3 -hybridized, and are free from steric crowding. These features of the quinuclidine structure explain some of the physical and chemical properties and peculiarities of quinuclidine and its derivatives. For example, quinuclidine is a volatile crystalline compound with a high melting point (158°). It rapidly and completely sublimes on standing in the open air. Removal of the symmetry (by turning to condensed systems or by introducing alkyl substituents) decreases the melting point (see Table I).

²⁰ M. V. Rubtsov, *Zh. Obshch. Khim.* **30**, 1498 (1960).

²¹ M. Luckner, *Pharmazie* **18**, 93 (1963).

Some interesting results were obtained by comparative investigation of the infrared (IR) spectra of quinuclidine, *N*-substituted piperidines, and piperazines.²⁷ Monocyclic compounds gave at 2700–2800 cm^{-1} characteristic absorption bands attributable to interaction between the nitrogen lone-pair electrons and the neighboring axial CH bonds. Quinuclidine does not absorb in this region, probably because of the absence of such interaction in the quinuclidine ring. There are absorption bands characteristic of quinuclidine at 2430, 2915, and 3405 cm^{-1} .²⁸

TABLE I
PHYSICAL PROPERTIES OF QUINUCLIDINES

Compound	Melting point (°C)	Boiling point (°C)	Ref.
Quinuclidine	158		22
2-Methylquinuclidine	Liquid	162–164	23
3-Methylquinuclidine	Liquid	169–171	24
4-Methylquinuclidine	49–50	158–163	25
Benzoquinuclidine	68–69		22
Dibenzoquinuclidine	111–112		26

The basicity of quinuclidine, which depends on the electron density at the nitrogen atom, is close to that of aliphatic amines and *N*-alkylpiperidines. In condensed benzo- and dibenzoquinuclidine systems the basicity decreases due to the inductive effect of the benzene rings.^{26, 29}

The influence of the rigid structure on the basicity of quinuclidine derivatives³⁰ is demonstrated by comparison of the pK_a values of benzo- and dibenzoquinuclidines with the structurally allied diethylaniline and diphenylamine (see Table II).

²² J. Meisenheimer, *Ann. Chem.* **420**, 190 (1920).

²³ R. Lukeš and I. Paleček, *Collection Czech. Chem. Commun.* **29**, 1582 (1964).

²⁴ V. Prelog, *Ann. Chem.* **545**, 229 (1940).

²⁵ R. Lukeš and M. Ferles, *Chem. Listy* **47**, 689 (1953).

²⁶ S. Krogt and B. M. Wepster, *Rec. Trav. Chim.* **74**, 161 (1955).

²⁷ M. V. Rubtsov, L. N. Yakhontov, and E. E. Mikhlin, *Zh. Obshch. Khim.* **35**, 621 (1965).

²⁸ L. G. Johnson, *J. Chem. Phys.* **33**, 949 (1960).

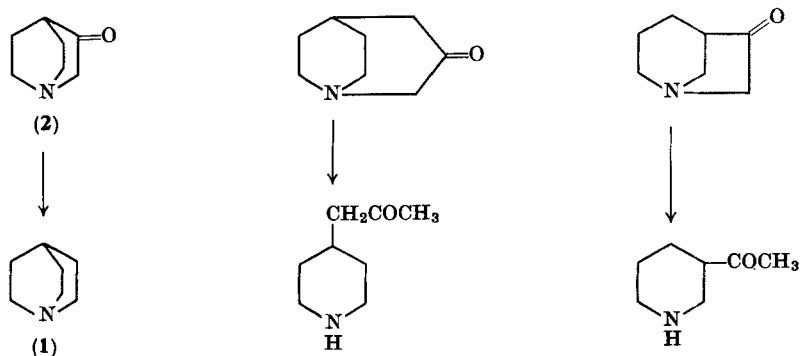
²⁹ B. M. Wepster, *Rec. Trav. Chim.* **71**, 1159 (1952).

³⁰ E. M. Arnett and C. J. Wu, *Chem. Ind.* (London) 1488 (1959).

TABLE II
BASICITY OF QUINUCLIDINES AND RELATED
COMPOUNDS

Compound	pK _a	Ref.
Dimethylamine	10.77	31
Diethylamine	10.93	31
Triethylamine	10.87	31
N-Methylpiperidine	10.08	31
Quinuclidine	10.58	26
Benzoquinuclidine	7.79	26
Diethylaniline	6.56	31
Dibenzoquinuclidine	4.46	26
Diphenylamine	0.79	31

Similar to other tertiary aliphatic amines, quinuclidine easily forms salts with mineral and organic acids, and quaternary derivatives with alkyl halides. However, the rates of reaction of alkyl iodides with quinuclidine are significantly higher than with tertiary aliphatic amines.³² For example, quinuclidine reacts with methyl iodide 50 times faster, and with isopropyl iodide 700 times faster, than does triethylamine. The addition compound of trimethylborane with quinuclidine is more stable than the corresponding adducts of trialkylamines. These results can be explained by the almost total



³¹ A. Albert and E. Serjeant, "Ionization Constants, a Laboratory Manual," Methuen, London, 1962.

³² H. C. Brown and S. Sujishi, *J. Am. Chem. Soc.* **70**, 2878 (1948).

absence of steric hindrance at the nitrogen lone-pair of the bicyclic compound.

The unusual structural features of quinuclidine give it a remarkable chemical stability. It is unchanged on heating with concentrated mineral acids (HCl, HI, H₂SO₄, HNO₃) and on treatment with potassium permanganate.²² Leonard *et al.*³³ found that the quinuclidine ring is preserved on Clemmensen reduction of quinuclid-3-one (2), whereas with other 1-azabicyclic ketones ring opening takes place.

Quinuclidine is not dehydrogenated by treatment with mercuric acetate, apparently because this process should go through a Δ^1 -dehydroquinuclidinium salt, which violates Bredt's rule.^{2, 34} Quinuclidine can be dehydrogenated only under vigorous conditions (300°) by treatment with palladium on carbon, or selenium.³⁵ In these cases C-N bond fission with formation of 4-ethylpyridine take place.

Pyrolysis and hydrogenolysis of quaternary quinuclidinium salts lead to high yields of quinuclidine.^{2, 36-38} Formation of the tertiary amines (in these cases aliphatic alcohols split off) is also the main by-process accompanying the Hofmann degradation of quaternary quinuclidinium bases.³⁹⁻⁴¹ Unsubstituted quinuclidine, for example, was isolated in 35% yield, together with quinuclidine ring-fission products, e.g., 1-methyl-4-vinylpiperidine and 4-(β -hydroxyethyl)-1-methylpiperidine, by Hofmann degradation of 1-methylquinuclidinium hydroxide.³⁹ These results also illustrate the stability of the ring system.

Quinuclidine *N*-oxides form *O*-acylium salts stable to hydrolysis in neutral and acid media [Eq. (1)]. Their sensitivity to alkalies, on the other hand, is very high and they can be titrated as dibasic acids.⁴²

³³ N. J. Leonard, I. W. Curry, and I. I. Sagura, *J. Am. Chem. Soc.* **75**, 6349 (1953).

³⁴ J. Bredt, *Ann. Chem.* **437**, 1 (1924).

³⁵ V. Prelog and K. Balenovic, *Chem. Ber.* **74**, 1508 (1941).

³⁶ R. Lukeš, *Collection Czech. Chem. Commun.* **14**, 655 (1949).

³⁷ R. Lukeš and I. Ernest, *Collection Czech. Chem. Commun.* **14**, 665 (1949).

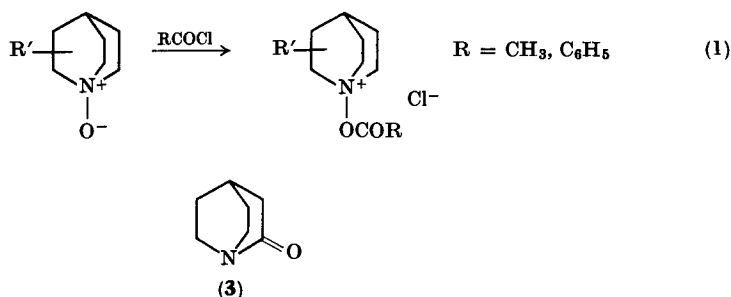
³⁸ T. Perrine, *J. Org. Chem.* **22**, 1484 (1957).

³⁹ R. Lukeš, O. Štrouf, and M. Ferles, *Collection Czech. Chem. Commun.* **22**, 1173 (1957).

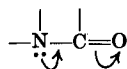
⁴⁰ J. Paleček, *Collection Czech. Chem. Commun.* **31**, 1340 (1966).

⁴¹ J. Paleček and Z. Polivka, *Collection Czech. Chem. Commun.* **32**, 3909 (1967).

⁴² R. Huisgen and W. Kolbeck, *Tetrahedron Letters* 783 (1965).



Interesting chemical properties were discovered in such bicyclic amides as quinuclidin-2-one (3).⁴³⁻⁴⁶ In this type of compound the axis of the nitrogen p electrons is orthogonal to the π electrons of the carbonyl group. As a result the necessary condition for conjugation, i.e., parallel axes of π and p electrons with maximum overlap, is not observed. This is why the conjugation of type



characteristic of common amides, is absent in quinuclidin-2-ones.

These structural peculiarities make some properties of quinuclidin-2-ones closer to those of aminoketones than of amides. The nitrogen of quinuclidin-2-one is easily protonated (common amides and lactams are O -protonated) and can be methylated. They are very basic (pK_a 5.33–5.6)⁴⁴ compared with other amides (e.g., N -acetyl-piperidine, pK_a 0.4).

Carbonyl group frequencies for quinuclidin-2-ones are on the average 80 cm^{-1} higher than for common lactams, and integral intensities of the same absorptions are nearly half those of quinuclidin-2-ones. Ultraviolet (UV) absorption maxima for quinuclidin-2-ones are midway between those for amides and ketones. On account of the lack of amide mesomerism quinuclidin-2-ones gain in reactivity. This is shown by the rather high rates of hydrolysis of such compounds

⁴³ L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.* **27**, 72 (1957).

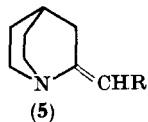
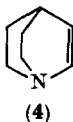
⁴⁴ H. Pracejus, *Chem. Ber.* **92**, 988 (1959).

⁴⁵ H. Pracejus, M. Kehlen, H. Kehlen, and H. Matschiner, *Tetrahedron* **21**, 2257 (1965).

⁴⁶ O. A. Reutov, "Teoreticheskie principy organicheskoi khimii" (The Theoretical Principles of Organic Chemistry), p. 85. Moskovskii Universitet, Moscow, 1964.

and the alcoholysis of their hydrochlorides. The kinetics of these reactions can be measured polarographically (common amides and lactams are polarographically inactive). A CH_2 group next to the carbonyl group in quinuclidin-2-one is rather acidic and the protons can be exchanged by deuterium. Finally, carbonyl groups of quinuclidin-2-ones undergo reactions such as oxime formation with hydroxylamine,⁴³ a general property of ketones rather than amides.

Unsaturated quinuclidine derivatives, e.g., Δ^2 -dehydroquinuclidine (4)^{47, 48} and its 2-substituted derivatives,⁴⁹ and quinuclidines with a semicyclic double bond at position 2 (5),⁴⁹ also display some unusual properties, behaving differently from common tertiary enamines. For example, dehydroquinuclidine does not have the characteristic absorption for enamines at $230\text{ m}\mu$ and is not hydrolyzed under mild conditions by dilute acids.



Fragmentation of quinuclidine derivatives,⁵⁰⁻⁵⁷ in contrast to the same process with aliphatic and bicyclic compounds without nitrogen, gives only one product. The solvolysis of 2-bromo-2-(quinuclidin-3-yl)propane (6) has a stepwise mechanism,⁵⁰⁻⁵⁷ and the degradation of 4-bromoquinuclidine (7) is synchronous.^{50, 53}

Ease of protonation of the quinuclidine nitrogen makes competitive reactions such as carbonium ion isomerization and substitution and elimination processes unimportant.

⁴⁷ C. A. Grob, A. Kaiser, and E. Renk, *Helv. Chim. Acta* **40**, 2170 (1957).

⁴⁸ C. A. Grob, A. Kaiser, and E. Renk, *Chem. Ind. (London)* 598 (1957).

⁴⁹ V. Braschler, C. A. Grob, and A. Kaiser, *Helv. Chim. Acta* **46**, 2646 (1963).

⁵⁰ C. A. Grob, *Angew. Chem.* **69**, 680 (1957).

⁵¹ C. A. Grob and F. Ostermayer, *Helv. Chim. Acta* **45**, 1119 (1962).

⁵² C. A. Grob, R. M. Holgerle, and M. Ohta, *Helv. Chim. Acta* **45**, 1823 (1962).

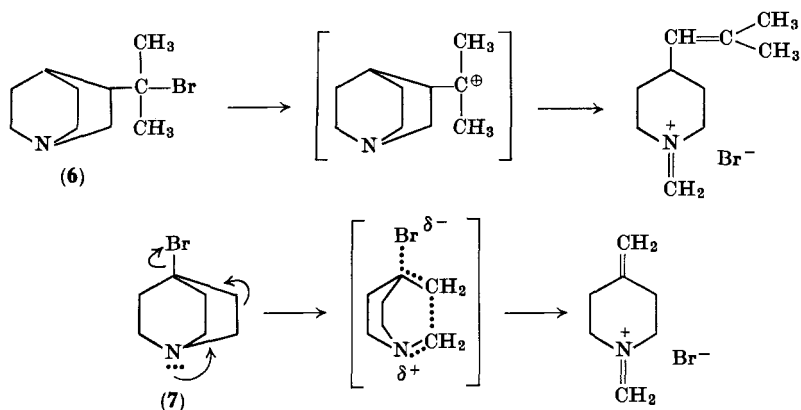
⁵³ P. Brenneisen, C. A. Grob, R. A. Jackson, and M. Ohta, *Helv. Chim. Acta* **48**, 146 (1965).

⁵⁴ C. A. Grob, *Angew. Chem.* **77**, 459 (1965).

⁵⁵ C. A. Grob, *Bull. Soc. Chim. France* 1360 (1960).

⁵⁶ C. A. Grob, *Angew. Chem.* **73**, 758 (1961).

⁵⁷ C. A. Grob, *Gazz. Chim. Ital.* **92**, 902 (1962).



III. Syntheses of Quinuclidine and Its Derivatives

After many years of investigation a great number of quinuclidine derivatives have been synthesized. Synthetic methods described in the literature for the preparation of quinuclidine and its derivatives and methods for building up quinuclidine bicyclic systems are separated in this review from those for substituent introduction into preformed quinuclidine rings. Reactions involving quinuclidine ring expansion with formation of derivatives of other 1-azabicycloalkanes are gathered into a special section.

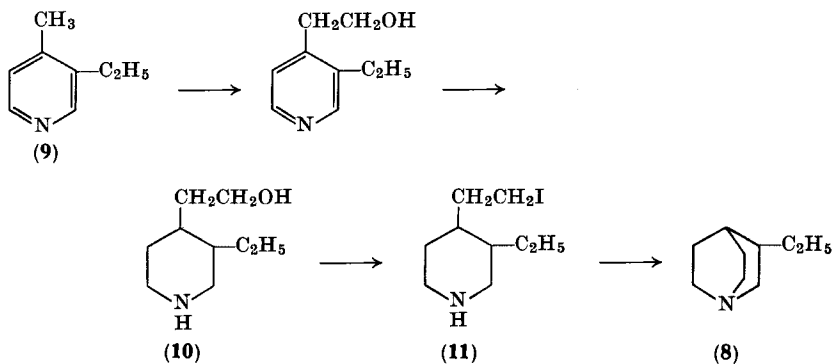
A. METHODS OF BUILDING UP QUINUCLIDINE SYSTEMS

Piperidine derivatives and acyclic substances such as trihalogenoalkanes and dihalogenoalkylamines may be used as starting materials. The piperidine derivatives are obtained mainly from pyridine compounds. Dihalogenoalkylamines and trihalogenoalkanes are prepared from tetrahydropyran derivatives, dialkoxy-substituted malonic esters, or alkane-tetracarboxylic esters.

1. Syntheses from Piperidine Intermediates

Quinuclidine ring formation starting from piperidine derivatives is carried out usually by (a) intramolecular alkylation or acylation or (b) intramolecular Dieckmann condensation.

a. *C-N Ring Closure*. Intramolecular alkylation was used in 1904 by Koenigs^{58, 59} for the preparation of the first synthetic quinuclidine derivative, 3-ethylquinuclidine (8). The starting material was



3-ethyl-4-methylpyridine (9). Hydroxymethylation of 9 was followed by reduction to 10 by sodium and alcohol. The hydroxy group in the piperidine derivative (10) was replaced by iodine and the 3-ethyl-4-(β -iodoethyl)piperidine (11) was cyclized by potassium carbonate to yield 3-ethylquinuclidine (8).

The similar scheme starting from 4-methylpyridine was used in 1909 by Löffler and Stitzel⁶⁰ for the synthesis of unsubstituted quinuclidine. These authors could not isolate the pure compound, which was first obtained 11 years later by Meisenheimer,²² who also described a transformation of 4-methylquinoline into benzoquinuclidine. Later, the intramolecular alkylation of 4-(β -haloalkyl)-piperidines was used for other syntheses of quinuclidine⁶¹ and its derivatives. 2- and 4-methylquinuclidines (12),^{23, 62, 63} and (13)²⁵, dibenzoquinuclidine (14),²⁶ 3-hydroxymethyl-3-methylquinuclidine (15),^{36, 37, 64} and 3-carboxymethyl-3-hydroxymethylquinuclidine lactone (16),⁶⁵ were prepared by this method.

⁵⁸ W. Koenigs, *Chem. Ber.* **37**, 3244 (1904).

⁵⁹ W. Koenigs and K. Bernhart, *Chem. Ber.* **38**, 3049 (1905).

⁶⁰ K. Löffler and F. Stitzel, *Chem. Ber.* **42**, 124 (1909).

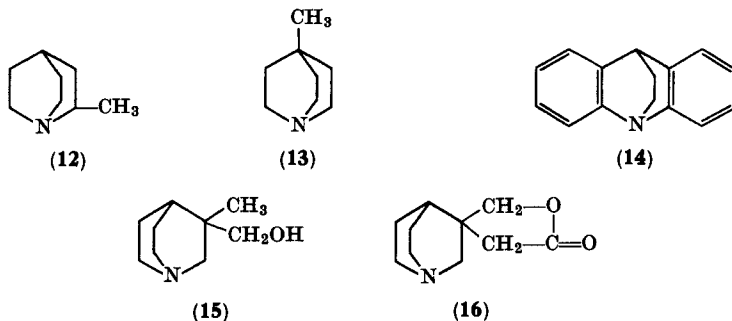
⁶¹ M. V. Rubtsov and V. A. Volskova, *Zh. Obshch. Khim.* **19**, 1378 (1949).

⁶² K. Winterfeld, *Arch. Pharm.* **268**, 308 (1930).

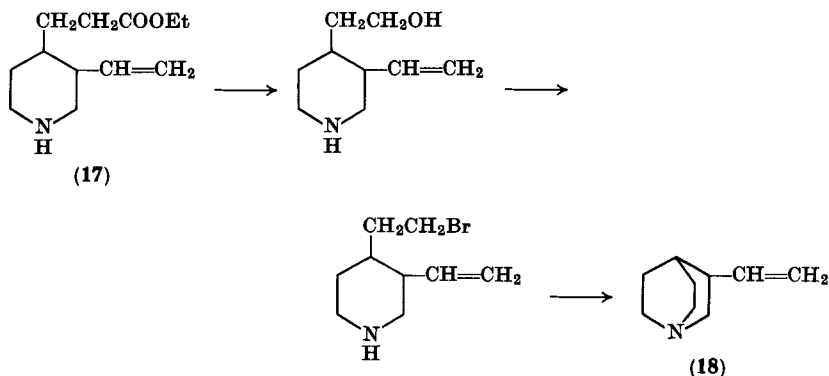
⁶³ J. Paleček and Z. Polivka, *Collection Czech. Chem. Commun.* **31**, 4592 (1966).

⁶⁴ R. Lukeš and V. Galik, *Collection Czech. Chem. Commun.* **21**, 620 (1956).

⁶⁵ E. E. Mikhlin and M. V. Rubtsov, *Zh. Obshch. Khim.* **27**, 691 (1957).



A similar method was used by Lukeš and Galik⁶⁶ to convert meroquinene ethyl ester (17), obtained from natural cinchonine, into the optically active 3-vinylquinuclidine (18).

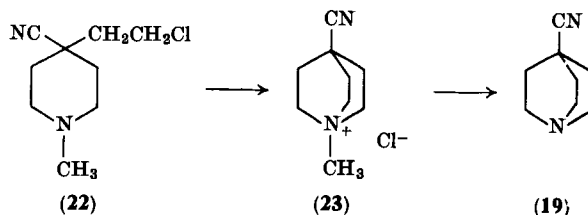


Grob and co-workers^{67, 68} applied Koenigs' scheme to the preparation of 4-substituted quinuclidines, including 4-cyano- (19), 4-bromo- (7), and 4-hydroxyquinuclidines (20). Cyclization in these cases was made with tertiary *N*-substituted (*N*-methyl and *N*-benzyl)piperidines (21 and 22). For example, 4-(β -chloroethyl)-4-cyano-1-methylpiperidine (22), obtained by condensation of 4-cyano-1-methylpiperidine with ethylene dichloride, was cyclized to 4-cyano-1-methylquinuclidinium chloride (23), from which methyl chloride splits off by heating to 260–270° *in vacuo*.⁶⁷

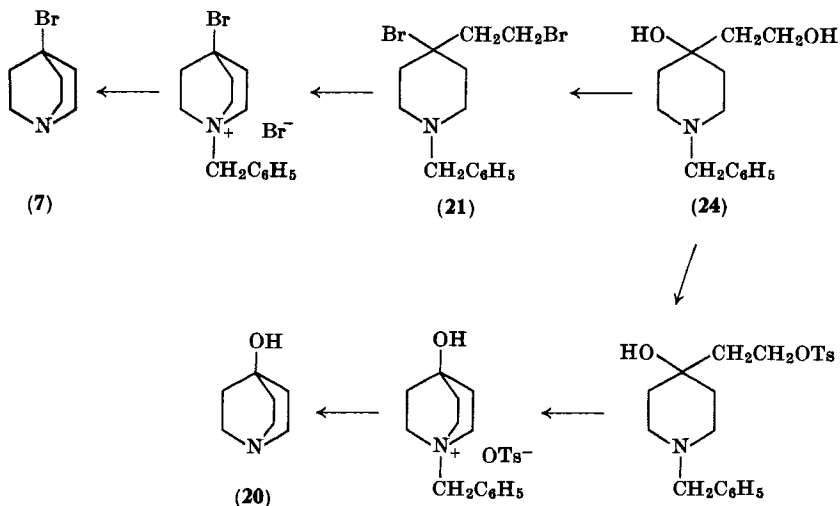
⁶⁶ R. Lukeš and V. Galik, *Chem. Listy* **47**, 858 (1953).

⁶⁷ C. Grob and E. Renk, *Helv. Chim. Acta* **37**, 1672 and 1681 (1954).

⁶⁸ C. Grob and P. Brenneisen, *Helv. Chim. Acta* **41**, 1184 (1958).



The similar transformations of 1-benzyl-4-hydroxy-4-(β -hydroxyethyl)piperidine (24) to 4-bromo- (7) and 4-hydroxyquinuclidines (20)⁶⁸ are given in the following scheme:



Rabe^{69, 70} and others,⁷¹⁻⁷⁵ carrying out syntheses of quinine analogs and isomers, used this method for building up the quinuclidine ring. In these cases the starting compounds were halo-ketone deriva-

⁶⁹ P. Rabe and G. Hagen, *Chem. Ber.* **74**, 636 (1941).

⁷⁰ P. Rabe and W. Schuler, *Chem. Ber.* **76**, 318 (1943).

⁷¹ V. Prelog, R. Seiwerth, S. Heimbach-Juhasz, and P. Stern, *Chem. Ber.* **74**, 647 (1941).

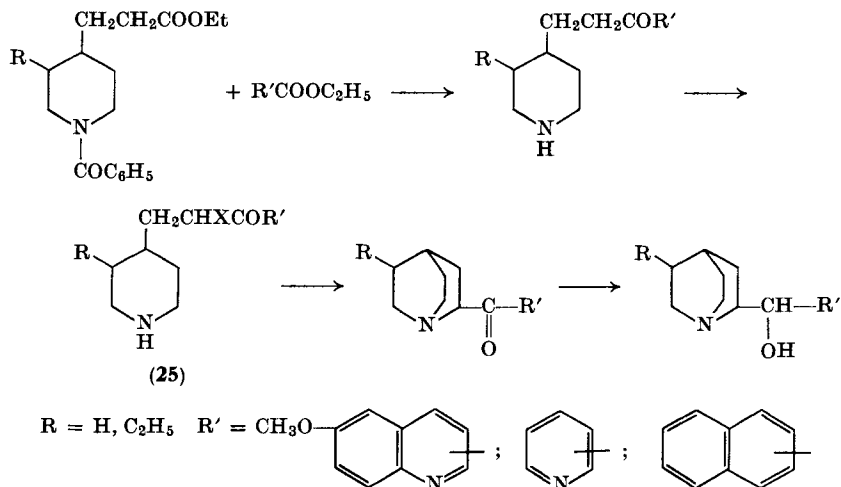
⁷² M. V. Rubtsov, *Zh. Obshch. Khim.* **9**, 1493 (1939).

⁷³ M. V. Rubtsov, *Zh. Obshch. Khim.* **13**, 593 and 702 (1943).

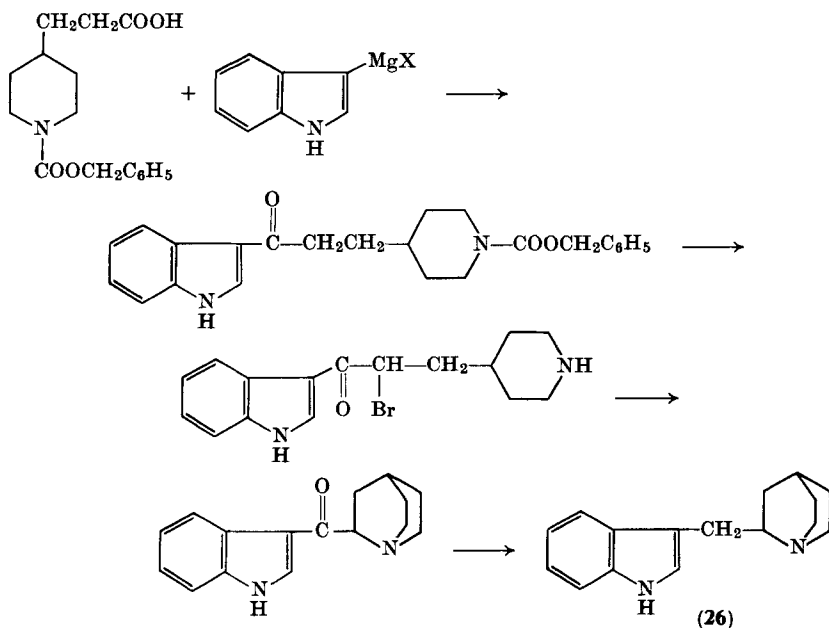
⁷⁴ M. V. Rubtsov, *Zh. Obshch. Khim.* **26**, 461 (1946).

⁷⁵ M. V. Rubtsov and N. A. Volskova, *Zh. Obshch. Khim.* **23**, 1685, 1688, and 1893 (1953).

tives of the piperidine series, e.g., 4-(γ -oxo- β -haloalkyl)piperidines (**25**). Syntheses and reactions of **25** are given in the following scheme:

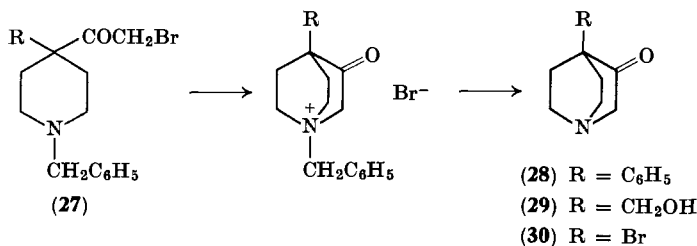


An analogous route was used for the preparation of 2-skatyl-quinuclidine (**26**)⁷⁶:



⁷⁶ I. J. De Grow and I. G. Kennedy, *J. Heterocyclic Chem.* **3**, 90 (1966).

Different types of oxohalopiperidine derivatives, e.g., **27** were used as starting material for the formation of 3,4-disubstituted quinuclidines: 3-oxo-4-phenyl-(**28**),³⁸ 4-hydroxymethyl-3-oxo- (**29**),⁷⁷ and 4-bromo-3-oxoquinuclidines (**30**).⁷⁸



It was found⁷⁸ that quinuclidine ring closure takes place only if both the 4-bromoacetyl group and the nitrogen lone-pair electrons are in the axial position. Formation of this conformation in a transition state is facilitated by the introduction of bulky substituents at position 4 and at the piperidine nitrogen. Attempts to cyclize compounds without such bulky substituents (e.g., 4-bromoacetyl-piperidine) fail.⁷⁸

A slightly different way for closing the quinuclidine ring was discovered by Rabe^{79, 80} for the synthesis of quinine alkaloids containing a vinyl group. In this case introduction of a halogen into oxoalkyl groups of 4-oxoalkyl-3-vinylpiperidines (**31**) without reaction at the vinyl double bond is difficult. That is why *N*-bromo- rather than *C*-bromo-substituted piperidines were used for quinuclidine ring closures.

Quinotoxine (**31**) yielded *N*-bromoquinotoxine (**32**), on treatment with sodium hypobromite, which by reaction with alkoxide was converted into the corresponding quinuclidine derivative—quininone (**33**). Rabe's method was applied to the total synthesis of quinine (**34**)¹⁸ and several of its analogs.^{81, 82}

⁷⁷ A. T. Nielsen, *J. Org. Chem.* **31**, 1053 (1966).

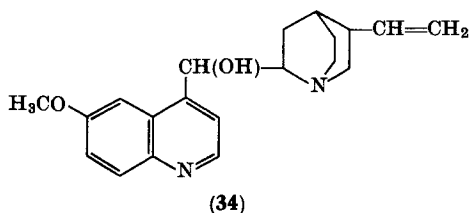
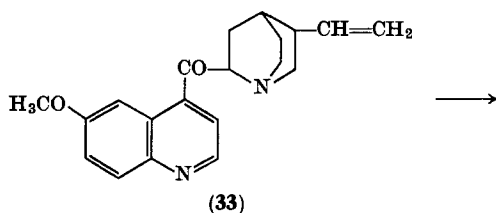
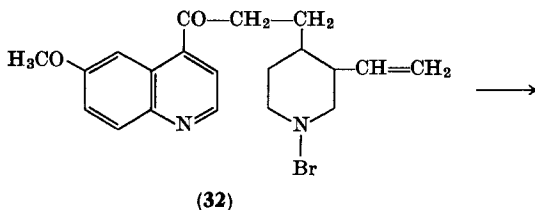
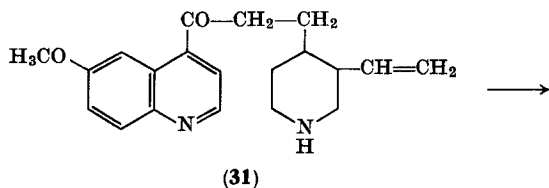
⁷⁸ F. J. Carrol, A. M. Ferguson, and J. B. Lewis, *J. Org. Chem.* **31**, 2957 (1966).

⁷⁹ P. Rabe, *Chem. Ber.* **44**, 2088 (1911).

⁸⁰ P. Rabe and K. Kindler, *Chem. Ber.* **51**, 446 (1918).

⁸¹ P. Rabe, W. Huntenburg, A. Schultze, and G. Volger, *Chem. Ber.* **64**, 2487 (1931).

⁸² G. Clemo and S. Popli, *J. Chem. Soc.* 1406 (1951).



In contrast to the cyclization of *N*-halogeno-4-(oxoalkyl)-piperidines, closure of the quinuclidine ring starting from 4-alkyl-*N*-halogenopiperidines met with difficulties. Application of the Hofmann–Loeffler reaction to 4-alkyl-*N*-chloropiperidines by Wawżonek, Lukeš, Ferles, and co-workers^{83–88} led to a mixture of

⁸³ S. Wawżonek, M. F. Nelson, and P. J. Thelen, *J. Am. Chem. Soc.* **73**, 2806 (1951).

⁸⁴ S. Wawżonek, M. F. Nelson, and P. J. Thelen, *J. Am. Chem. Soc.* **74**, 2894 (1952).

⁸⁵ R. Lukeš and M. Ferles, *Collection Czech. Chem. Commun.* **20**, 1227 (1955).

⁸⁶ R. Lukeš and M. Ferles, *Collection Czech. Chem. Commun.* **16**, 416 (1951).

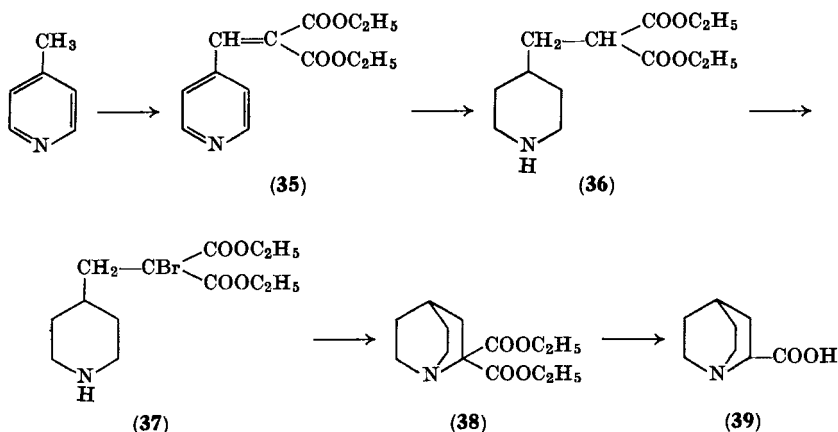
⁸⁷ S. Wawżonek and T. C. Wilkinson, *J. Am. Chem. Soc.* **88**, 1732 (1966).

⁸⁸ R. Lukeš and J. Paleček, *Collection Czech. Chem. Commun.* **29**, 1582 (1964).

quinuclidine derivatives and the isomeric alkyl 1-azabicyclo[2.2.1]-heptanes.

The reaction of *N*-(β -chloroethyl)piperidine or its derivatives with methanolic potassium hydroxide⁸⁹ yields Hofmann degradation products²⁷ (mainly 1,2-bis(*N*-piperidino)ethane) of 1,4-bis(pentamethylenepiperazinium) dichloride which is evidently the initial product rather than quinuclidine compounds.

Koenigs' method for quinuclidine ring closure was applied by Rubtsov^{90, 91} and Grob^{92, 93} to the intramolecular alkylation of α -halogeno acids and esters of piperidines. Rubtsov and Dorokhova⁹⁰ developed a simple five-step method for the synthesis of quinuclidine-2-carboxylic acid (39).



Condensation of γ -picoline with mesoxalic ester yielded 4-(β,β -diethoxycarbonylvinyl)pyridine (35). The unsaturated ester (35) was hydrogenated with platinum catalyst to form 36 which was treated with bromine. 4-(β -Bromo- β,β -diethoxycarbonyl)ethylpiperidine (37) was obtained and was cyclized with pyridine to 2,2-diethoxycarbonylquinuclidine (38). Hydrolysis of 38 and partial decarboxylation gave quinuclidine-2-carboxylic acid (39).

⁸⁹ A. S. Sadykov, M. Karimov, and Kh. A. Aslanov, *Zh. Obshch. Khim.* **33**, 3414 and 3417 (1963); **34**, 4104 (1964).

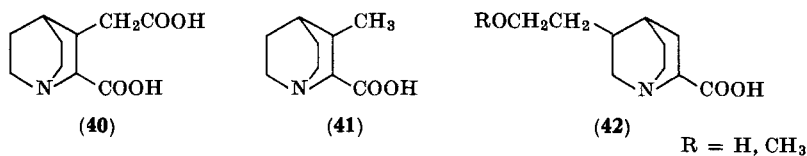
⁹⁰ M. V. Rubtsov and M. I. Dorokhova, *Zh. Obshch. Khim.* **23**, 706 (1953).

⁹¹ M. V. Rubtsov and E. E. Mikhlin, *Zh. Obshch. Khim.* **25**, 2303 (1955).

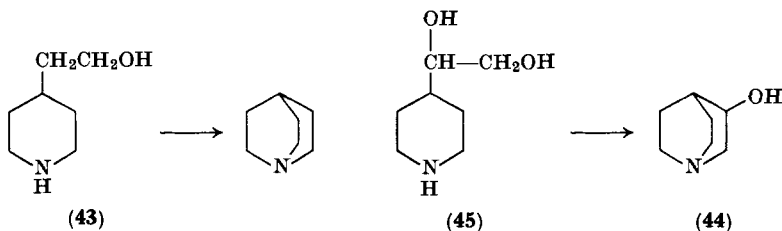
⁹² E. Renk and C. A. Grob, *Helv. Chim. Acta* **37**, 2119 (1954).

⁹³ CIBA, Ltd., British Patent 771,435 (1957); *Chem. Abstr.* **51**, 13941 (1957).

The above method of cyclization of α -halogenoesters of the piperidine series was widely used for the preparation of various 2,3- and 2,5-disubstituted quinuclidines: 3-carboxymethylquinuclidine-2-carboxylic acid (**40**),⁹⁴ 3-methylquinuclidine-2-carboxylic acid (**41**),⁹⁵ 5-(β -hydroxyethyl and β -methoxyethyl)quinuclidine-2-carboxylic acids (**42**).^{96, 97}



Leonard and Elkin's⁹⁸ cyclodehydration of 4-(β -hydroxyethyl)-piperidine (**43**) in the gas phase can be considered as an intramolecular alkylation. The same method was used for synthesis of 3-hydroxyquinuclidine (**44**) from 4-piperidylethane-1,2-diol (**45**).⁹⁹



Synthesis of 4-cyanoquinuclidine (**19**) by condensation of 1-alkyl-4-cyanopiperidines (**46**) with α,β -glycol esters in the presence of alkaline reagents¹⁰⁰ is another variant of this reaction.

⁹⁴ M. V. Rubtsov and E. E. Mikhlin, *Zh. Obshch. Khim.* **23**, 823 (1953).

⁹⁵ E. E. Mikhlin and M. V. Rubtsov, *Zh. Obshch. Khim.* **27**, 77 (1957).

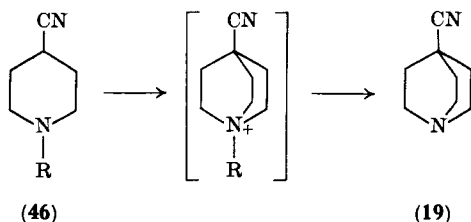
⁹⁶ M. V. Rubtsov and L. N. Yakhontov, *Zh. Obshch. Khim.* **25**, 1183 (1955).

⁹⁷ M. V. Rubtsov and L. N. Yakhontov, *Zh. Obshch. Khim.* **25**, 1743 (1955).

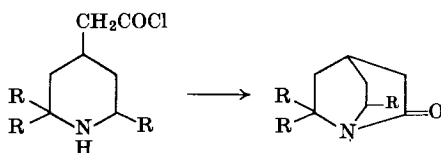
⁹⁸ S. Leonard and S. Elkin, *J. Org. Chem.* **27**, 4635 (1962).

⁹⁹ H. S. Aaron, O. O. Owens, P. D. Rosenstock, S. Leonard, S. Elkin, and J. Miller, *J. Org. Chem.* **30**, 1331 (1965).

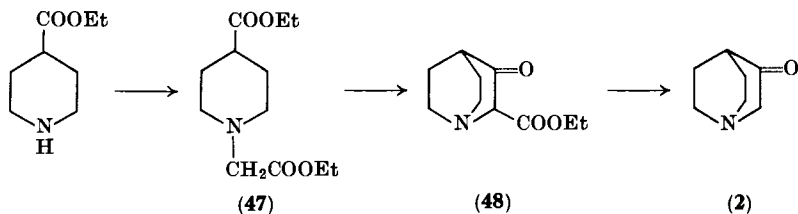
¹⁰⁰ CIBA, Ltd., British Patent 816,504 (1955); *J. Appl. Chem. (London)* **10**, ii, 288 (1960).



Intramolecular acylation in piperidines also is used to build up a quinuclidine ring. By this method Yakhontov and Rubtsov,⁴³ and later Pracejus,^{44, 45, 101} synthesized quinuclidin-2-one (3) and its 6,6-dimethyl and 6,6,7-trimethyl derivatives, starting from the corresponding acid chlorides, by the action of potassium carbonate or tertiary amines.



b. C-C Ring Closure. The second scheme for quinuclidine ring closure, based on intermolecular Dieckmann condensation, was used by Clemo and Metcalfe for the preparation of quinuclidin-3-one (2).¹⁰² Ethyl isonipecotinate was converted into ethyl 1-ethoxycarbonylmethylisonipecotinate (47) by alkylation with chloroacetic ester. The diester (47) was cyclized with potassium in toluene to β -ketoester (48) which was treated without isolation with hydrochloric acid for saponification and decarboxylation.

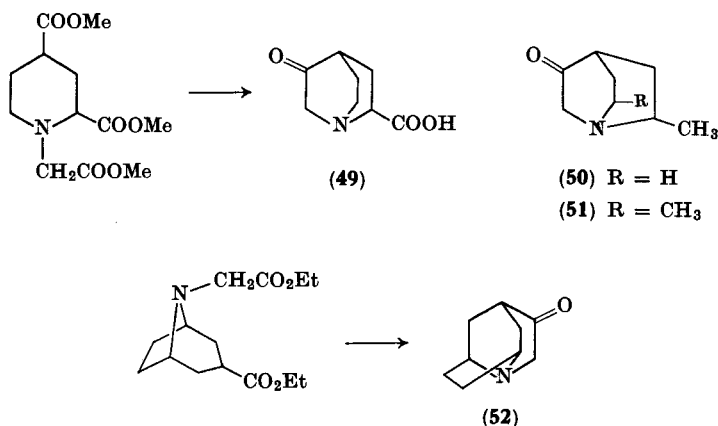


¹⁰¹ H. Pracejus, *Chem. Ber.* **98**, 2897 (1965).

¹⁰² G. Clemo and T. Metcalfe, *J. Chem. Soc.* 1989 (1937).

This scheme was later developed and the yield of ketone (2) from 47 was increased to 84%.¹⁰³⁻¹⁰⁷ Isolation of the intermediate ethyl 3-ketoquinuclidine-2-carboxylate (48)¹⁰⁸ gave rise to methods for the preparation of various 2,3-disubstituted quinuclidines.^{49, 108, 109}

Clemo's method was used in subsequent syntheses of substituted quinuclidinones: 5-ketoquinuclidine-2-carboxylic acid (49),¹¹⁰ 6-methyl- (50),¹¹¹ and 6,7-dimethylquinuclidin-3-ones (51),¹¹² as well as tropoquinuclidine derivatives (52).¹¹³



¹⁰³ L. Sternbach and S. Kaiser, *J. Am. Chem. Soc.* **74**, 2215 (1952).

¹⁰⁴ E. E. Mikhлина and M. V. Rubtsov, *Zh. Obshch. Khim.* **29**, 118 (1959).

¹⁰⁵ L. Sh. Gorodetskii, V. Ja. Vorob'eva, V. I. Zeifman, Yu. G. Zelinskii, Z. M. Klimonova, E. E. Mikhлина, and M. V. Rubtsov, Russian Patent 158,882 (1963); *Chem. Abstr.* **60**, 11993 (1964); U.S. Patent 3,342,828 (1967); Swiss Patent 4,138,843 (1967).

¹⁰⁶ M. V. Rubtsov, E. E. Mikhлина, and V. Ja. Vorob'eva, Russian Patent 134,265 (1960); *Chem. Abstr.* **55**, 14486 (1961).

¹⁰⁷ M. V. Rubtsov, E. E. Mikhлина, V. Ja. Vorob'eva, D. I. Lobanov, and N. A. Komarova, Russian Patent 149,106 (1962).

¹⁰⁸ L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.* **29**, 2343 (1959).

¹⁰⁹ E. E. Mikhлина, M. V. Rubtsov, and V. Ja. Vorob'eva, *Zh. Obshch. Khim.* **31**, 3251 (1961).

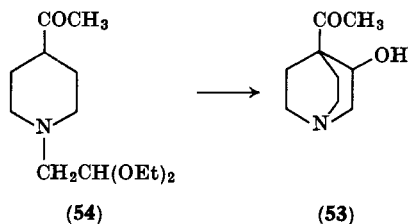
¹¹⁰ L. N. Yakhontov, L. I. Mastafanova, and M. V. Rubtsov, *Zh. Obshch. Khim.* **30**, 519 (1960).

¹¹¹ E. E. Mikhлина, V. Ja. Vorob'eva, and M. V. Rubtsov, *Zh. Obshch. Khim.* **33**, 3852 (1963).

¹¹² M. V. Rubtsov, E. E. Mikhлина, V. Ja. Vorob'eva, and N. A. Komarova, *Zh. Obshch. Khim.* **34**, 2218 (1964).

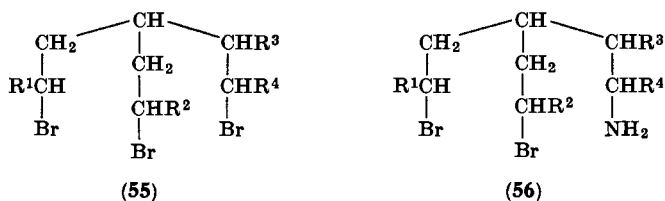
¹¹³ W. Schneider and F. Schumann, *Tetrahedron Letters* 1583 (1966).

A special case in quinuclidine ring closure is the synthesis of quinuclidine compounds by intramolecular aldol condensation used for the preparation of 4-acetylquinuclidin-3-ol (**53**) from 4-acetyl-1-(2',2'-diethoxyethyl)piperidine (**54**).⁷⁷



2. Syntheses from Acyclic Compounds

Another approach to the synthesis of quinuclidine and its derivatives was found by Prelog,^{114, 115} based on the action of ammonia on tribromoalkanes (**55**) under pressure at 110°–120° or on twofold intramolecular alkylation by treatment of dibromoalkylamines (**56**) with alkali.



These methods were used for the preparation of quinuclidine,^{39, 114–117} 2-,^{23, 24} 3-²⁴ and 4-alkylquinuclidines,²⁵ and quinuclidine-2-carboxylic acid.¹¹⁸ Prelog's attempts to prepare quinine analogs by quinuclidine ring closure starting from the tribromoalkyl derivative (**57**) failed.¹¹⁹

¹¹⁴ V. Prelog, U.S. Patent 2,192,840; *Chem. Abstr.* **34**, 4396 (1940).

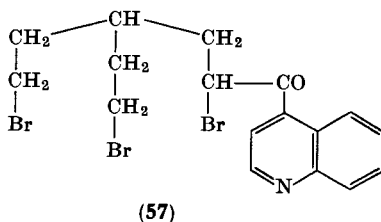
¹¹⁵ V. Prelog, British Patent 517,830 (1940); French Patent 91,940; *Chem. Abstr.* **35**, 6984 (1941).

¹¹⁶ V. Prelog, A. Kohlbach, E. Cerkovnikov, A. Režek, and M. Piantaniela, *Ann. Chem.* **532**, 69 (1937).

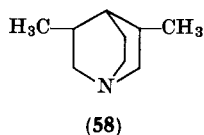
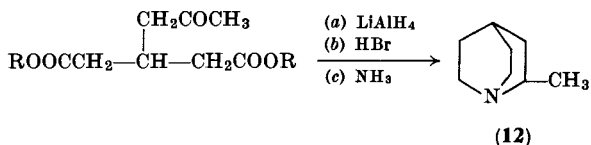
¹¹⁷ V. Prelog, E. Cerkovnikov, and G. Ustricev, *Ann. Chem.* **535**, 37 (1938).

¹¹⁸ V. Prelog and E. Cerkovnikov, *Ann. Chem.* **532**, 83 (1937).

¹¹⁹ V. Prelog, R. Seiwerth, V. Hahn, and E. Cerkovnikov, *Chem. Ber.* **72**, 1325 (1939).

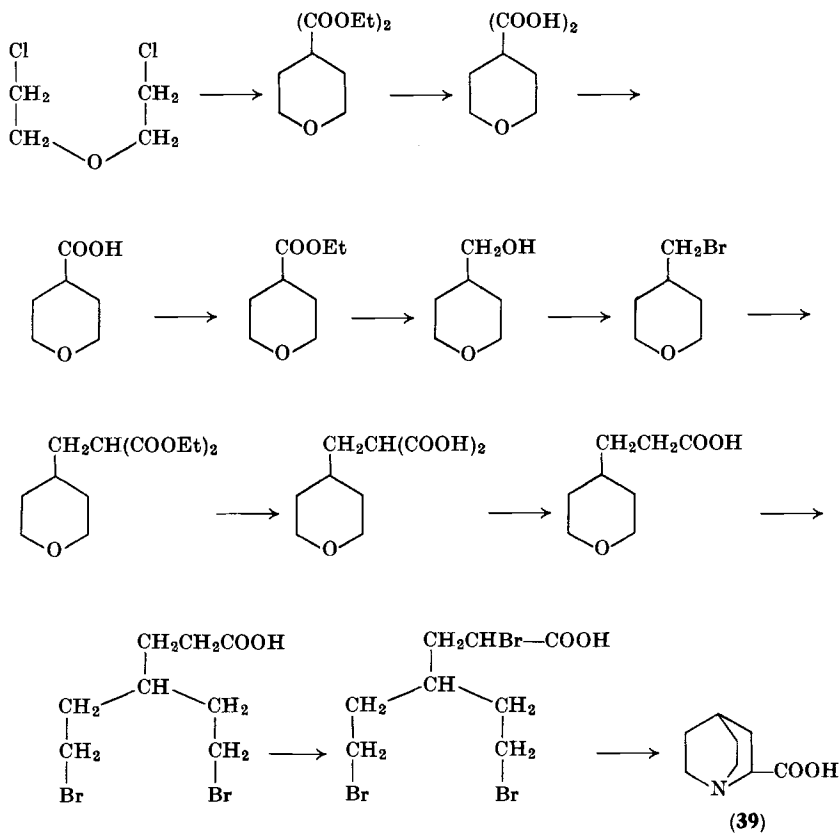


Comparison of the synthetic methods for the preparation of quinuclidine derivative starting from piperidines and tribromoalkanes and dibromoalkylamines shows that in some cases Prelog's scheme gives better results, while in others intramolecular alkylation, acylation, or Dieckmann cyclization are more useful. For example, the best yield (37%) of 2-methylquinuclidine (**12**)²³ and the only known 3,5-disubstituted quinuclidine, 3,5-dimethylquinuclidine,¹²⁰ (**58**) were synthesized by Prelog's method.



However, the preparation of quinuclidine derivatives starting from tribromoalkanes and dibromoalkylamines may be difficult because the starting compounds require multistage syntheses resulting in poor yields. Prelog's scheme is also less useful for the formation of quinuclidine derivatives with functional groups, e.g., quinuclidine-2-carboxylic acid (**39**),¹¹⁸ which requires twelve steps with overall yield of only 4%. In the five-step synthesis starting from γ -picoline the yield is 30%.⁹⁰

¹²⁰ J. Paleček and H. Šípalová, *Collection Czech. Chem. Commun.* **30**, 547 (1965).



B. METHODS OF INTRODUCING SUBSTITUENTS INTO THE QUINUCLIDINE RING

Quinuclidine is a saturated bicyclic system. Introduction of functional groups in this molecule by methods of direct substitution offers considerable difficulties and no such investigations are known.

For this reason reactive groups are usually introduced before quinuclidine ring closure and various transformations are effected afterward. The carboxyl and carbonyl derivatives, e.g., quinuclidine-2-carboxylic acid, quinuclidin-3-one, and so on, are useful compounds containing such functional groups. Nearly all substituted quinuclidines were obtained from their carboxylic acids and carbonyl derivatives by common synthetic methods.

1. *Syntheses of Substituted Quinuclidines from Quinuclidinecarboxylic Acids*

At the present time quinuclidine 2-,^{90, 118} 3-,^{121, 122} and 4-mono-carboxylic acids^{67, 100} are known as well as quinuclidine-2- carboxylic acids with various substituents at positions 3^{95, 108} or 5^{96, 110} and quinuclidine-3-carboxylic acids substituted at positions 2¹²³ or 6.¹¹¹ Only one compound with two carboxylic groups in the quinuclidine ring, the 2,3-dicarboxylic acid, has been described.¹⁰⁹ Homologs of many quinuclidinecarboxylic acids have been prepared, among which quinuclidine-3-acetic¹²⁴⁻¹²⁷ and 3-carboxymethylquinuclidine-2-carboxylic acids⁹⁴ are interesting for subsequent transformations.

One can divide syntheses of quinuclidine derivatives from quinuclidinecarboxylic acids into three main groups: (a) reactions without any changes in the carbon skeleton, (b) reactions including fission of quinuclidine carbon-carbon bonds, and (c) processes extending the carbon chain.

a. *Reactions without Any Changes in the Carbon Skeleton.* Quinuclidinecarboxylic acids easily form acyl halides, which can be converted without isolation into esters^{67, 96, 125, 128-130} or amides.^{125, 130, 131} For the preparation of esters of quinuclidinecarboxylic acids methods such as esterification in the presence of sulfuric acid or hydrogen chloride and transesterification with alkali metal alcoholates have also been successfully applied.^{96, 109, 110}

¹²¹ C. A. Grob and E. Renk, *Helv. Chim. Acta* **37**, 1689 (1954).

¹²² E. E. Mikhлина, V. Ja. Vorob'eva, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* **243** (1966).

¹²³ V. Ja. Furshtatova, E. E. Mikhлина, and M. V. Rubtsov, *Zh. Obshch. Khim.* **29**, 477 (1959).

¹²⁴ E. E. Mikhлина and M. V. Rubtsov, *Zh. Obshch. Khim.* **28**, 103 (1958).

¹²⁵ E. E. Mikhлина and M. V. Rubtsov, *Zh. Obshch. Khim.* **30**, 2970 (1960).

¹²⁶ E. E. Mikhлина and M. V. Rubtsov, *Zh. Obshch. Khim.* **32**, 2935 (1962).

¹²⁷ L. N. Yakhontov, L. I. Mastafanova, and M. V. Rubtsov, *Zh. Obshch. Khim.* **33**, 3211 (1963).

¹²⁸ M. V. Rubtsov, L. N. Yakhontov, and E. S. Nikitskaya, *Zh. Obshch. Khim.* **25**, 2311 (1955).

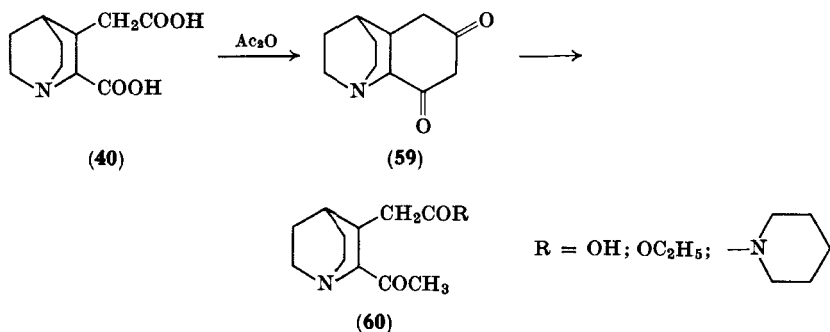
¹²⁹ M. V. Rubtsov, E. S. Nikitskaya, and V. S. Usovskaya, *Zh. Obshch. Khim.* **26**, 130 (1956).

¹³⁰ M. V. Rubtsov, I. M. Sharapov, M. D. Mashkovskii, E. E. Mikhлина, E. S. Nikitskaya, V. Ja. Vorob'eva, and V. S. Usovskaya, *Česk. Farm.* **13**, 299 (1964).

¹³¹ M. V. Rubtsov, E. S. Nikitskaya, E. E. Mikhлина, A. D. Janina, and V. Ja. Furshtatova, *Zh. Obshch. Khim.* **23**, 1555 (1953).

Δ^2 -Dehydroquinuclidinyl-2- and 3-carboxamides were formed from the corresponding esters by the action of alcoholic ammonia.^{47, 49} Quinuclidinecarboxylic esters were also used in the preparation of hydrazides and their hydrazones,^{95, 132} and the amides in the synthesis of nitriles.^{47, 49, 90}

Attempts to prepare an anhydride from 3-carboxymethylquinuclidine-2-carboxylic acid (**40**) in the presence of acetic anhydride and sodium acetate led unexpectedly to the tricyclic β -diketone (**59**).¹³³ This reacts with compounds containing active hydrogen (water, alcohols, and amines) to yield 2-acetylquinuclidine-3-acetic acid derivatives (**60**).¹³³



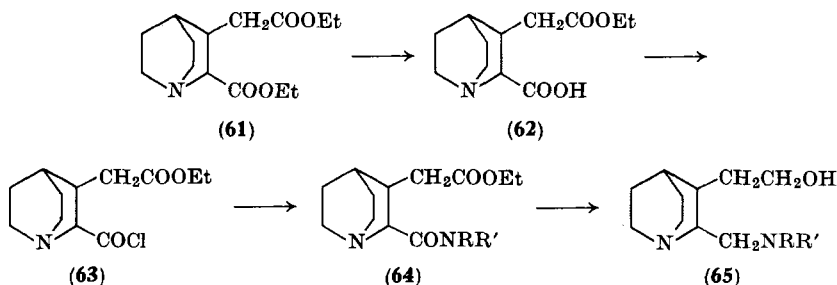
Quinuclidinecarboxylic esters easily undergo saponification. This process is especially easy for α -alkoxycarbonyl groups.¹³⁴ Aqueous solutions of ethyl 3-ethoxycarbonylmethylquinuclidine-2-carboxylate (**61**) on standing at room temperature form the monoester (**62**).¹³⁴ This was used for the syntheses of compounds with different functional groups at positions 2 and 3 of the quinuclidine ring. For example, treatment of 3-ethoxycarbonylmethylquinuclidine-2-carboxylic acid (**62**) with thionyl chloride gives the monochloride (**63**), which with primary and secondary amines (**63**) forms 3-ethoxycarbonylmethylquinuclidine-2-carboxamides (**64**).^{130, 134} Reduction of these amido-

¹³² E. S. Nikitskaya, E. E. Mikhlin, L. N. Yakhontov, and V. Ja. Furshtatova, *Zh. Obshch. Khim.* **28**, 2786 (1958).

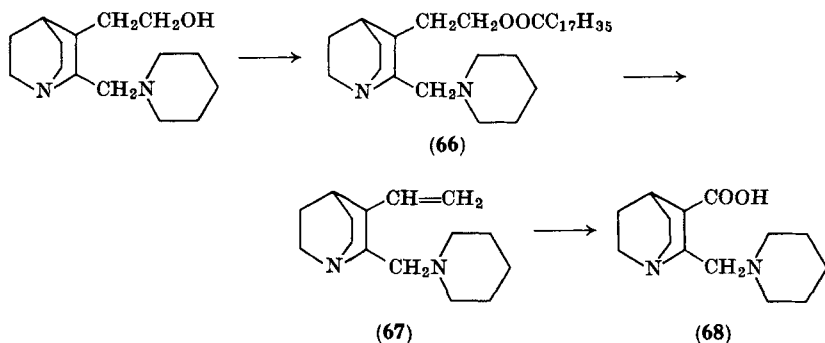
¹³³ E. E. Mikhlin, V. Ja. Vorob'eva, M. V. Rubtsov, and G. G. Dvoryantseva, *Zh. Obshch. Khim.* **35**, 110 (1965).

¹³⁴ M. V. Rubtsov, E. E. Mikhlin, and V. Ja. Furshtatova, *Zh. Obshch. Khim.* **24**, 2217 (1954).

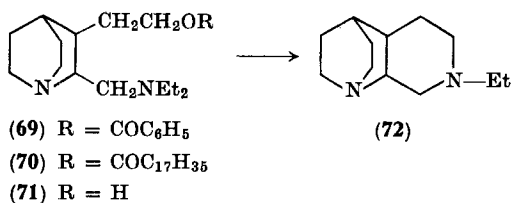
esters by LiAlH_4 gave 2-alkyl (or dialkyl)aminoethyl-3-hydroxyethylquinuclidines (**65**).



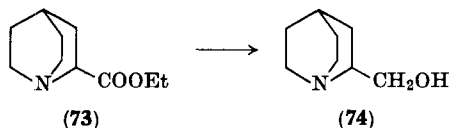
3-(β -Stearoyloxyethyl)-2-(*N*-piperidinomethyl)quinuclidine (**66**) was converted by Kraft's reaction into an unsaturated compound (**67**) which formed 2-*N*-piperidinomethylquinuclidine-3-carboxylic acid (**68**) by oxidation with potassium permanganate.¹²³



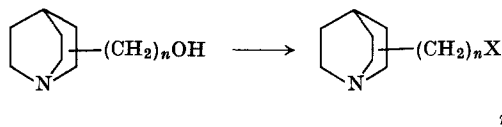
Formation of quinuclidine-3-carboxylic acid derivatives (**68**) from these reactions was conclusive proof of saponification of the ethoxycarbonyl group at position 2 of the diester (**61**). A similar reaction takes place with diethyl quinuclidine-2,3-dicarboxylate.¹⁰⁹ This is in agreement with the known principle of easier saponification of α - than β -amino acid esters. Some 3-(β -acyloxyethyl)-2-diethylaminomethylquinuclidines (**69**, **70**)¹²³ on distillation at atmospheric pressure cyclize with loss of ester and formation of a new tricyclic system, quinuclidino[2,3-*c*]piperidine (**72**). The same reaction takes place by heating the corresponding amino alcohol (**71**) with phthalic anhydride in the presence of benzenesulfonic acid.¹²³



Reduction of ethyl quinuclidine-2-carboxylate (73) by the Bouveault method or with LiAlH_4 yields 2-hydroxymethylquinuclidine (74).²⁴ The second way is more convenient, gives better yields, and has been more widely used.^{67, 95, 121, 125, 134}



Halogenoalkylquinuclidines were prepared by the reaction of the corresponding alcohols with thionyl chloride or halogen acids.^{24, 49, 121, 135, 136}



The halogen atoms of 2-halomethylquinuclidines are not reactive enough to be useful; 2-chloromethylquinuclidine, for example, does not react with ammonia or amines,¹³⁷ while the corresponding reactions of 2-bromomethylquinuclidine give poor yields.¹³⁷ Halogen atoms in 3-haloalkylquinuclidines are more active; nevertheless, the use of these compounds as starting materials for various syntheses is hampered by their ease of conversion into polymeric quaternary salts.¹³⁶ The above peculiarities of quinuclidine halogeno derivatives limit their use to reactions with strong nucleophilic reagents. Therefore, the general method of preparation of aminoalkylquinuclidines is by reduction of the corresponding quinuclidinecarboxamides by LiAlH_4 , and not by reaction between quinuclidine halogeno derivatives and amines.^{122, 130, 131, 138}

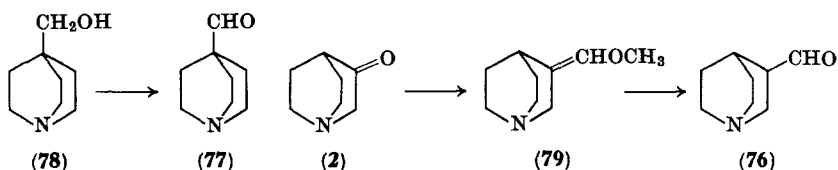
¹³⁵ E. Rajner, E. Cerkovnikov, and P. Stern, *Arch. Pharm.* **281**, 78 (1943).

¹³⁶ I. Ernest, *Collection Czech. Chem. Commun.* **15**, 322 (1950).

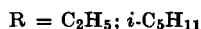
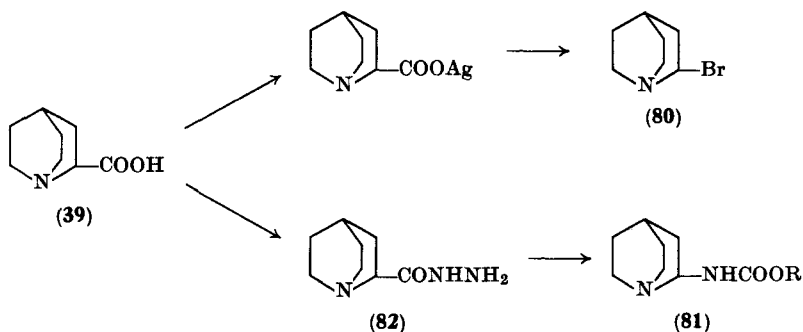
¹³⁷ V. Prelog, E. Rajner, and P. Stern, *Helv. Chim. Acta* **26**, 1172 (1943).

¹³⁸ M. V. Rubtsov and E. S. Nikitskaya, *Zh. Obshch. Khim.* **24**, 1659 (1954).

Quinuclidine aldehydes are important synthetic intermediates. All three monoformylquinuclidines are known: 2- and 3-formylquinuclidines (**75** and **76**) were prepared^{139, 140} by reduction of *N*-methylquinuclidinecarboxanilides with calculated amounts of LiAlH_4 or by reduction of ethyl quinuclidinecarboxylates with NaAlH_4 . 4-Formylquinuclidine (**77**) was made by oxidation of quinuclidyl-4-carbinol (**78**) with potassium dichromate.⁶⁷ 3-Formylquinuclidine (**76**) was also synthesized from quinuclidin-3-one (**2**) by reaction with methoxymethylene triphenylphosphorane and hydrolysis of the 3-methoxymethylenequinuclidine (**79**) with hydrochloric acid.¹⁴¹



b. *Reactions Involving Fission of Carbon-Carbon Bonds.* Starting from quinuclidine-2-carboxylic acid, 2-bromoquinuclidine (**80**)⁹⁰ and alkyl *N*-(2-quinuclidinyl)urethans (**81**)¹⁴² have been synthesized. These compounds are of interest because they have unusual combinations of functional groups on the same carbon atom: bromine and amino groups in 2-bromoquinuclidine and two amino groups in 2-aminoquinuclidine derivatives. Some new chemical properties thereby arise.



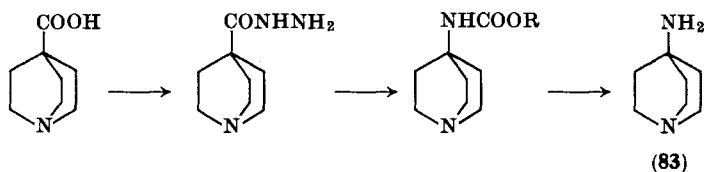
¹³⁹ M. V. Rubtsov and L. N. Yakhontov, *Zh. Obshch. Khim.* **25**, 2143 (1955).

¹⁴⁰ L. I. Mastafanova, L. N. Yakhontov, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* 858 (1965).

¹⁴¹ L. N. Yakhontov, L. I. Mastafanova, and M. V. Rubtsov, Russian Patent, 175,946 (1964); *Chem. Abstr.* **64**, 14174 (1966).

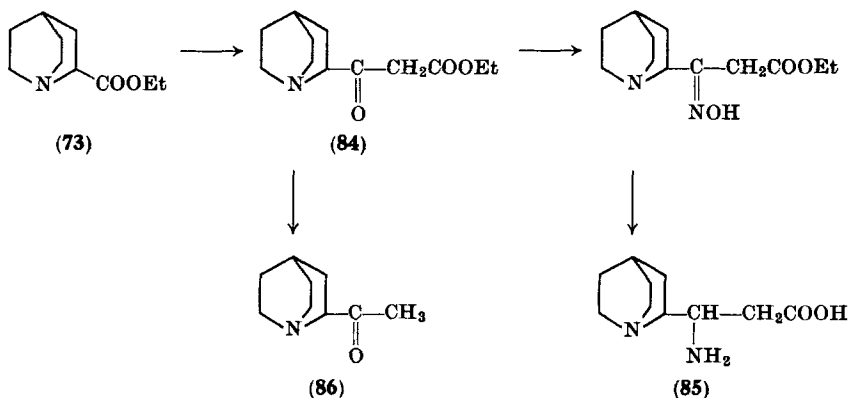
¹⁴² M. V. Rubtsov and E. E. Mikhlina, *Zh. Obshch. Khim.* **26**, 135 (1956).

For example, 2-bromoquinuclidine (**80**) does not form Grignard reagents and 2-aminoquinuclidine is so unstable that on hydrolysis of its urethans (**81**) under mild conditions ammonia is lost and polymers of dehydroquinuclidine are formed. The synthesis of 2-bromoquinuclidine (**80**) was achieved by the Borodin reaction,⁹⁰ and the urethans (**81**) were obtained from quinuclidine-2-carboxyhydrazide (**82**) by the Curtius reactions.¹⁴² The Curtius reaction with quinuclidine-4-carboxylic acid derivatives gave 4-aminoquinuclidine (**83**).¹⁴³ This compound (**83**) was also synthesized directly from quinuclidine-4-carboxylic acid by the Schmidt reaction. However, the first method is better, in spite of having more steps.



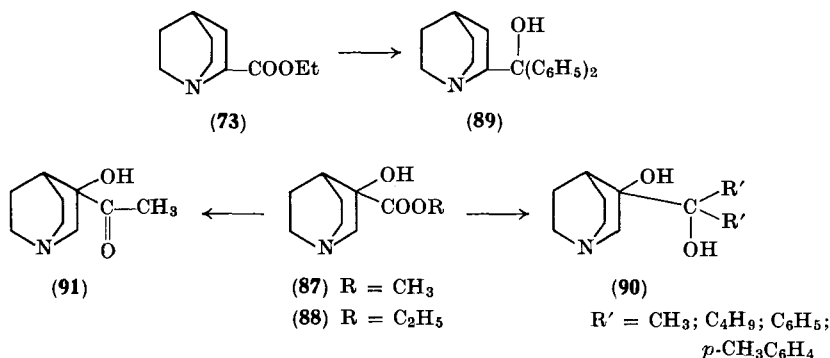
c. Processes Extending the Carbon Chain. Such syntheses of quinuclidine derivatives use Claisen condensations, Grignard reactions, etc.

Claisen condensation of ethyl quinuclidine-2-carboxylate (**73**) with ethyl acetate yields ethyl β -oxo- β -(2-quinuclidyl)propionate (**84**). This was transformed into β -amino- β -(2-quinuclidyl)propionic acid (**85**)¹⁰⁸ and 2-acetylquinuclidine (**86**).⁴³

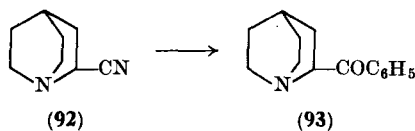


¹⁴³ E. E. Mikhlin and M. V. Rubtsov, Russian Patent, 189,861 (1966).

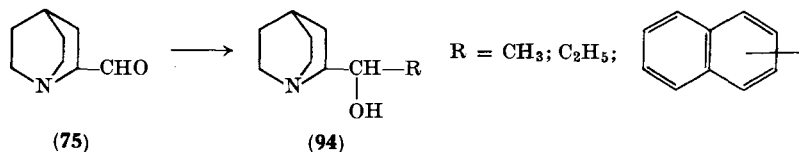
Grignard reactions on quinuclidine-2-carboxylic esters (**73**) and 3-hydroxyquinuclidine-3-carboxylic esters (**87** and **88**) gave the corresponding carbinols (**89**)²⁴ and pinacols (**90**).¹⁴⁴



In the reaction of the hydroxy ester (**87**) with methylmagnesium iodide the process stops at the ketone (**91**) stage. The pinacols were investigated under various pinacolone rearrangement conditions.¹⁴⁴ By a Grignard reaction of 2-cyanoquinuclidine (**92**), 2-benzoylquinuclidine (**93**) has been prepared.⁴⁹



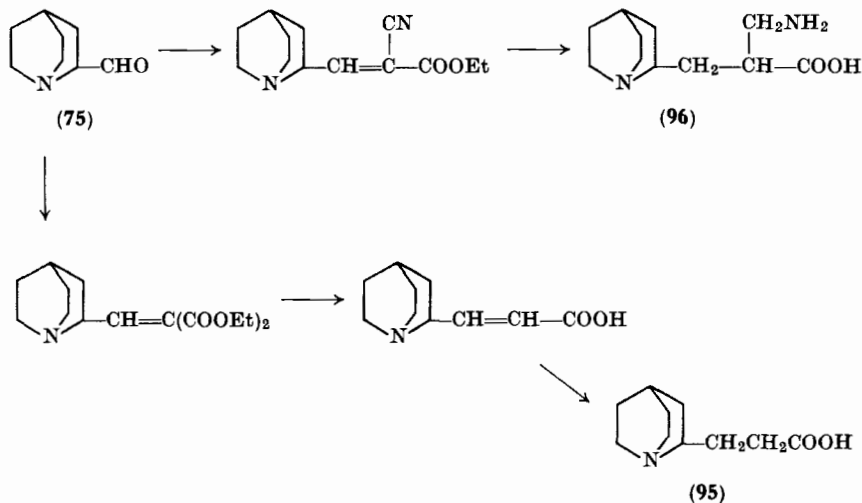
Use of 2-formylquinuclidine (**75**) in reactions with organomagnesium compounds led to a new method for the synthesis of quinuclid-2-ylcarbinols (**94**), which are quinine analogs.¹⁴⁵



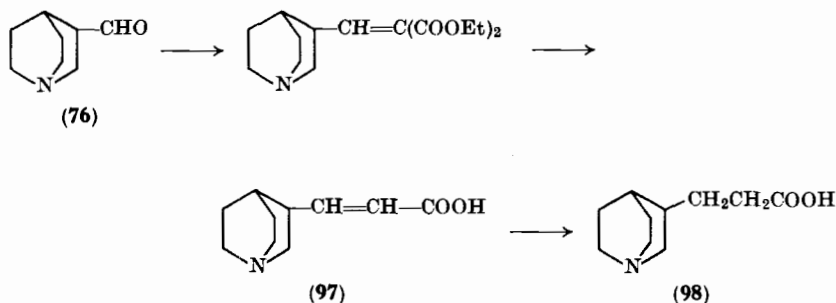
¹⁴⁴ E. E. Mikhlin, A. D. Janina, V. I. Sheichenko, Yu. N. Sheinker, and M. V. Rubtsov, *Zh. Organ. Khim.* **2**, 179 (1966).

¹⁴⁵ L. N. Yakhontov, S. V. Jatsenko, and M. V. Rubtsov, *Zh. Obshch. Khim.* **28**, 1177 (1958).

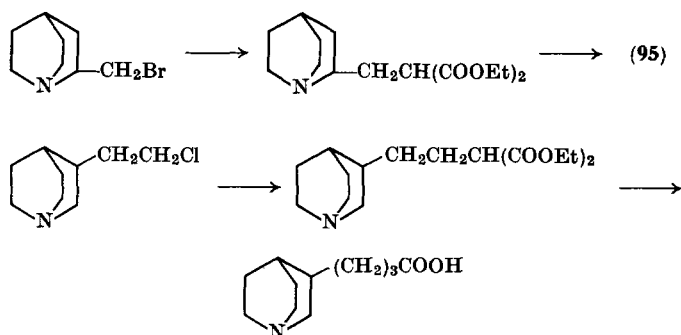
Knoevenagel condensation of 2-formylquinuclidine (**75**) with cyanoacetic¹⁰⁸ and malonic¹²⁹ esters was used to make β -(quinuclid-2-yl)propionic acid (**95**) and its α -aminomethyl derivative (**96**).



Similarly, 3-formylquinuclidine (**76**) was transformed into β -(quinuclid-3-yl)acrylic (**97**) and propionic acids (**98**).¹⁴⁰



The sodiomalonic ester synthesis was used in the preparation of β -(quinuclid-2-yl)propionic acid (**95**) starting from 2-bromomethylquinuclidine,¹²⁸ and γ -(quinuclid-3-yl)butyric acid from 3-(β -chloroethyl)quinuclidine.¹²⁵

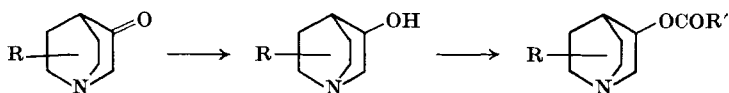


2. Syntheses of Substituted Quinuclidines from Quinuclidin-3-ones

Quinuclidin-3-one is the most easily accessible of the keto derivatives of quinuclidine. Quinuclidin-2-ones have been investigated less and at the present time are not much used as starting compounds for synthetic work.

Syntheses starting from quinuclidin-3-one are very diverse and may be divided into two main groups: (a) reactions without any change in carbon skeleton and (b) processes involving increase in the number of carbon atoms.

a. *Reactions without Any Changes in Carbon Skeleton.* Hydrogenation of quinuclidin-3-one or substituted quinuclidin-3-ones to the corresponding alcohols and their subsequent acylation led to various esters and urethans of quinuclidin-3-ol of biological interest.^{103, 111, 112, 146-151}



¹⁴⁶ L. Sternbach and S. Kaiser, *J. Am. Chem. Soc.* **74**, 2219 (1952).

¹⁴⁷ L. Randall, R. Stefko, and W. Benson, *J. Pharmacol. Exptl. Therap.* **104**, 284 (1952).

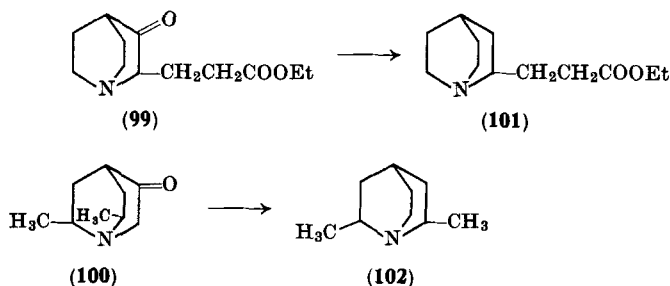
¹⁴⁸ L. Sternbach, British Patent 694,067; *Chem. Abstr.* **48**, 11498 (1954); Swiss Patent 295,534 (1954).

¹⁴⁹ R. Duschinsky, U.S. Patent 2,658,067; *Chem. Abstr.* **49**, 1823 (1955); British Patent 725,228 (1955); German (W) Patent 931,653 (1957).

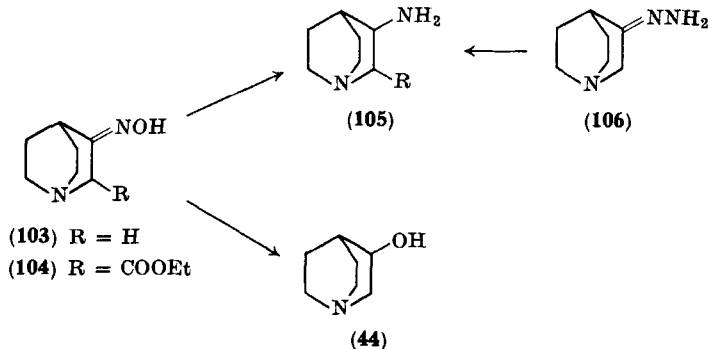
¹⁵⁰ E. E. Mikhlina and M. V. Rubtsov, *Zh. Obshch. Khim.* **30**, 163 (1960).

¹⁵¹ M. V. Rubtsov, M. D. Mashkovskiy, E. E. Mikhlina, K. A. Zaitseva, and V. Ja. Vorob'eva, *Med. Prom. SSSR*, No. 10, 14 (1962).

Quinuclidin-3-ol (**44**) was obtained by various methods of quinuclidin-3-one (**2**) reduction.^{33, 102} By Clemmensen³³ and Kishner¹⁵² reduction quinuclidine (**1**) was formed. The Kishner reduction of 2-substituted quinuclidin-3-ones was used to synthesize 2-monosubstituted quinuclidines, e.g., ethyl β -(2-quinuclidyl)-propionate (**101**)¹⁰⁴ and 6,7-dimethylquinuclidine (**102**)¹¹² from the corresponding 3-keto derivatives (**99** and **100**).



Oximes of quinuclidin-3-one (**103**)^{103, 122} and ethyl 3-ketoquinuclidine-2-carboxylate (**104**)¹⁰⁸ have been reduced to amines (**105**).

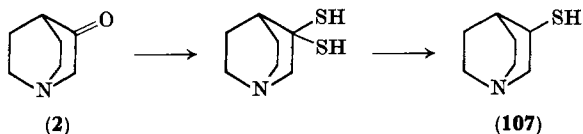


It was found that with quinuclidin-3-one oxime (**103**) reduction both in acidic and neutral media is accompanied by hydrolysis, and quinuclidin-3-ol (**44**) is formed together with 3-aminoquinuclidine (**105**; R = H). Reduction of quinuclidin-3-one hydrazone (**106**) yields only 3-aminoquinuclidine.

Treatment of quinuclidin-3-one (**2**) with hydrogen sulfide and then reduction by NaBH_4 forms 3-mercaptoquinuclidine (**107**).¹⁵³

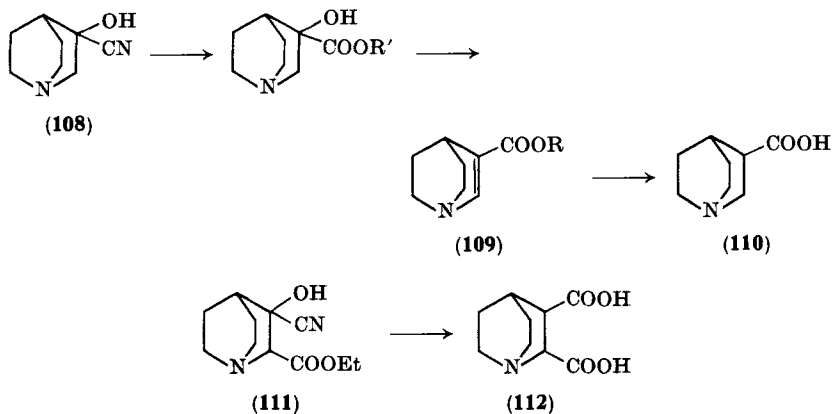
¹⁵² J. C. Kellett and C. W. Hite, *Pharm. J.* **54**, 883 (1965).

¹⁵³ K. Shaw, *Can. J. Chem.* **43**, 3112 (1965).



b. *Processes Involving Increase in the Number of Carbon Atoms.* Reactions between 3-oxoquinuclidines and potassium cyanide^{109, 121, 154} or acetone cyanohydrin¹²² were used to prepare quinuclidinone cyanohydrins.

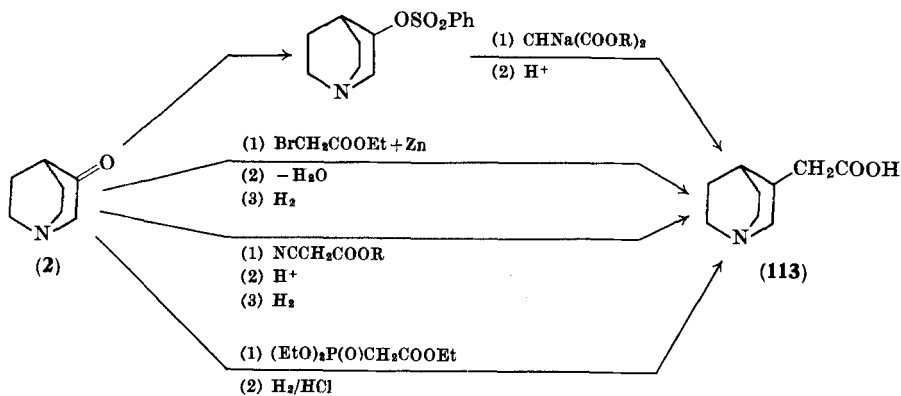
By hydrolysis and dehydration of quinuclidin-3-one cyanhydrin (108), 3-alkoxycarbonyl- Δ^2 -dehydroquinuclidines (109) were obtained, which can be reduced and saponified to quinuclidine-3-carboxylic acid (110).^{121, 122} Quinuclidine-2,3-dicarboxylic acid (112) was similarly prepared from 2-ethoxycarbonylquinuclidin-3-one cyanohydrin (111).¹⁰⁹



Various methods have been used to lengthen a carbon side chain, in the syntheses of quinuclidyl-3-acetic acid (113) (Scheme 1). The lowest yield is in the sodiomalonic ester synthesis (13.4%).¹²⁵ Much better results are afforded by the Reformatsky reaction (40%)¹²⁵ and Knoevenagel condensation (65–70%).¹²⁶ The best yield (nearly quantitative) may be obtained by application of the Wittig–Horner reaction.¹⁵⁵

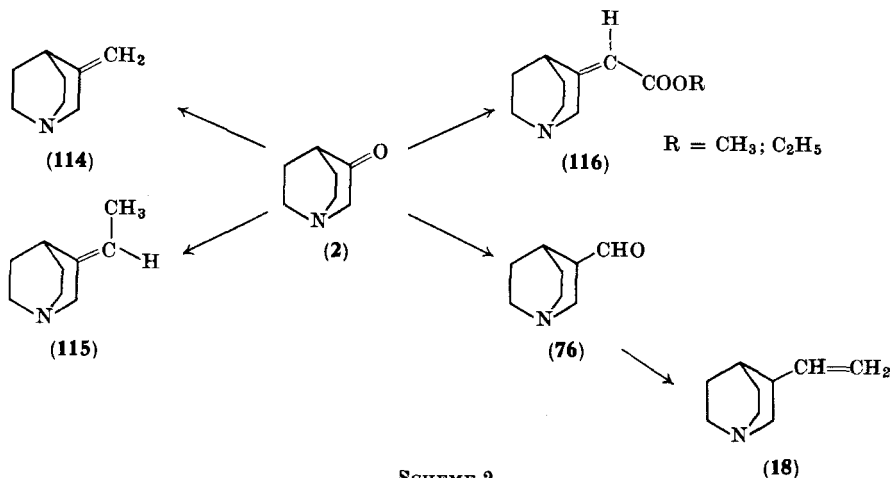
¹⁵⁴ C. A. Grob, Swiss Patent 328,904 (1958); *Chem. Abstr.* **53**, 7205 (1959).

¹⁵⁵ L. N. Yakhontov, L. I. Mastafanova, and M. V. Rubtsov, Russian Patent 164,286 (1963); *Chem. Abstr.* **61**, 16050 (1964).



SCHEME 1

Use of the Wittig and Horner reactions with quinuclidin-3-one (2) and other β -oxoquinuclidine derivatives afforded a variety of 3-substituted quinuclidines.^{127, 140, 155-157} Examples are the syntheses of 3-methylene- (114), 3-ethylidene- (115),¹⁵⁷ 3-alkoxycarbonylmethylene- (116),¹²⁸ and 3-formylquinuclidines (76)¹⁴⁰ (Scheme 2).



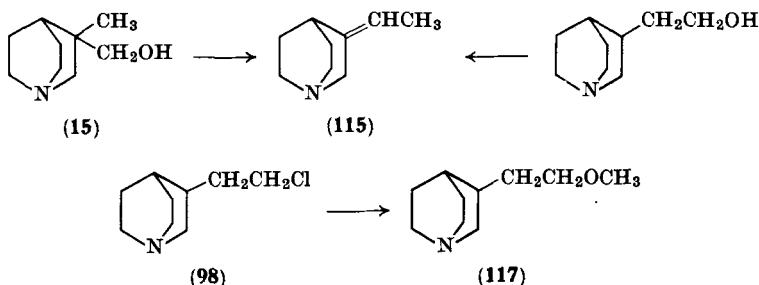
SCHEME 2

¹⁵⁶ L. N. Yakhontov, L. I. Mastafanova, S. L. Portnova, and M. V. Rubtsov, *Dokl. Akad. Nauk. SSSR* **162**, 1075 (1965).

¹⁵⁷ L. N. Yakhontov, L. I. Mastafanova, K. F. Turchin, Yu. N. Sheinker, and M. V. Rubtsov, *Dokl. Akad. Nauk SSSR* **168**, 1085 (1966).

Some of the above reactions have been shown to follow a stereoselective course.¹⁵⁷ The 3-ethylidenequinuclidine (**115**) is formed through an intermediate complex which has the methyl and α -methylene groups separated as far as possible. The stereochemistry of the 3-alkoxycarbonylmethylenequinuclidines (**116**) is determined by the interaction of the ring nitrogen atom with the alkoxycarbonyl group which leads to the isomer with these two groups on the same side of the double bond.

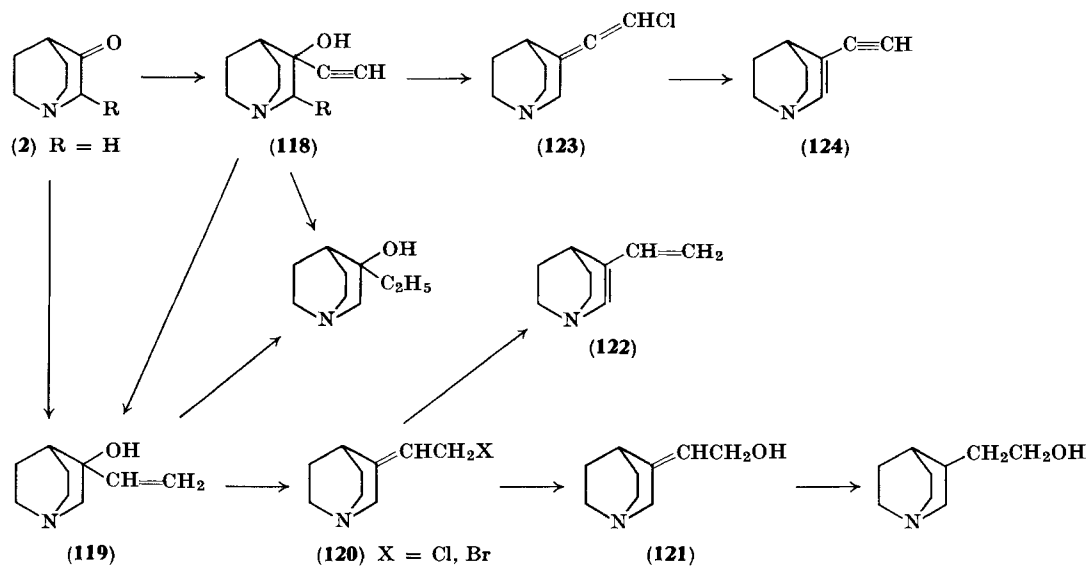
Double application of the Wittig reaction, first with methoxymethylenetriphenylphosphorane and then with methylenetriphenylphosphorane, converts quinuclidin-3-one (**2**) into 3-vinylquinuclidine (**18**) in 50% overall yield.¹⁵⁶ This method of introducing a vinyl group at the β -position is of great interest because other syntheses^{36, 37, 158, 159} either do not give unsaturated quinuclidine compounds or are accompanied by displacement of the double bond into the semicyclic position. For example, 3-ethylidenequinuclidine (**115**) was obtained instead of 3-vinylquinuclidine (**18**) by dehydrogenation accompanied by rearrangement of 3-hydroxymethyl-3-methylquinuclidine (**15**) and by treatment of 3-(β -hydroxyethyl)quinuclidine with phosphoric anhydride or concentrated hydrochloric acid. Reactions of 3-(β -halogenoethyl)quinuclidines with sodium hydroxide formed quaternary polymers, and 3-(β -methoxyethyl)quinuclidine (**117**) was formed from 3-(β -chloroethyl)quinuclidine (**98**) and methanolic potassium hydroxide under mild conditions.



In only one case, the dehydration of 3-(β -hydroxyethyl)quinuclidine with phthalic anhydride and benzenesulfonic acid, did Ernest succeed in isolating from the mixture of isomeric 3-ethylidene- (**115**)

¹⁵⁸ I. Ernest, *Collection Czech. Chem. Commun.* **15**, 486 (1950).

¹⁵⁹ R. Lukeš and I. Ernest, *Collection Czech. Chem. Commun.* **15**, 150 (1950).



SCHEME 3

and 3-vinylquinuclidines (**18**), the corresponding 3-vinyl derivative (**18**) by repeated recrystallization of the styphnate salts.¹⁵⁸

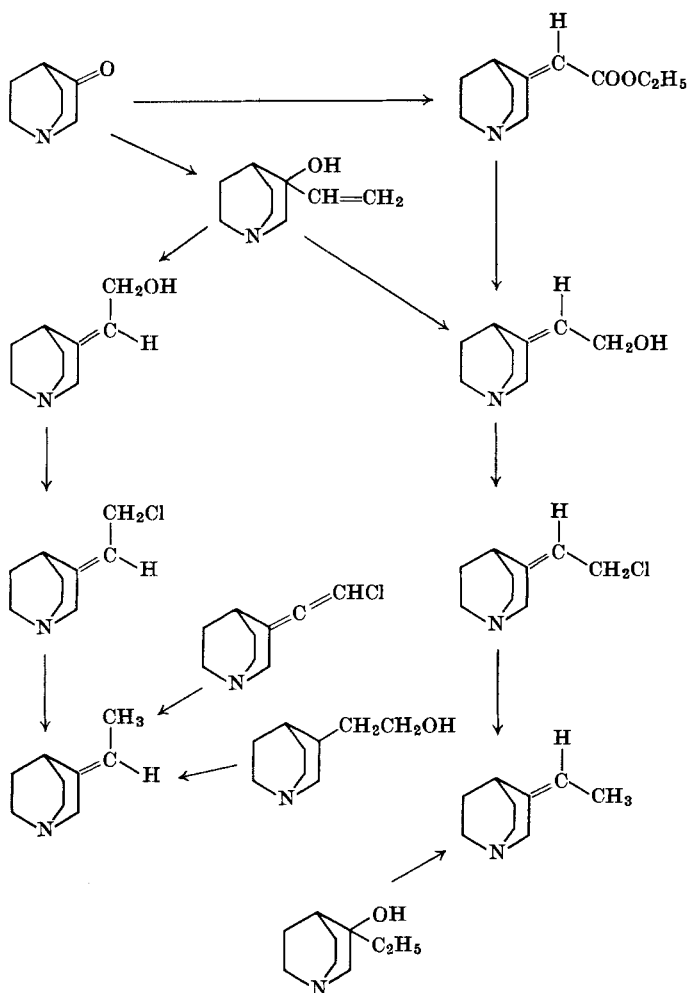
Reaction of quinuclidin-3-one (**2**) and its 2-substituted derivatives with acetylene yields 3-ethynyl-3-hydroxyquinuclidines¹⁶⁰ which are very readily hydrogenated to 3-ethyl-3-hydroxyquinuclidines.

Selective reduction of 3-ethynyl-3-hydroxyquinuclidine (**118**, R = H) yields 3-hydroxy-3-vinylquinuclidine (**119**).¹³⁶ This was also synthesized directly from quinuclidin-3-one (**2**) and vinylmagnesium bromide.¹⁶¹

Substitution of the hydroxy group in **119** by halogen with thionyl chloride or hydrobromic acid is accompanied by allylic rearrangement and yields 3-(β -halogenoethylidene)quinuclidines (**120**). 3-(β -Bromoethylidene)quinuclidine (**120**, X = Br) was converted into 3-(β -hydroxyethylidene)quinuclidine (**121**) and then into 3-(β -hydroxyethyl)quinuclidine.¹³⁶ By dehydrohalogenation of 3-(β -chloroethylidene)quinuclidine, 3-vinyl- Δ^2 -dehydroquinuclidine (**122**) was obtained.¹⁶¹ Similar processes with acetylene-allene rearrangement were also observed during the substitution of the hydroxy group by halogen in 3-hydroxy-3-ethynylquinuclidine (**118**, R = H). Here 3-(β -chlorovinylidene)quinuclidine (**123**)¹⁵⁷ was a product, from which hydrogen halide split off very easily to form 3-ethynyl- Δ^2 -dehydroquinuclidine (**124**) (Scheme 3).

In the course of investigations on allylic and acetylene-allene rearrangements of 3-substituted quinuclidines, it was found that by oxidation and ozonolysis of compounds with functional groups at positions allylic to the double bond, not only the double bonds but also the adjacent carbon-carbon bonds are broken. For example, in the oxidation of 3-hydroxy-3-vinylquinuclidine (**119**), with potassium permanganate under mild conditions, and in its ozonolysis, quinuclidin-3-one (**2**) is formed along with 3-hydroxyquinuclidine-3-carboxylic acid.¹⁶¹ The positions of double bonds in such systems can be firmly established by NMR spectroscopy, but not by oxidative methods.¹⁶¹

Various reactions of quinuclidin-3-one have led to the synthesis of two series of geometrical isomers of 3-substituted quinuclidines with semicyclic double bonds: 3-ethylidene,^{136, 157, 162} 3-(β -hydroxyethylidene)-,^{136, 157} and 3-(β -chloroethylidene)-quinuclidines¹⁵⁷ (Scheme 4). Some interconversions of compounds within each series were realized¹⁵⁷ and the configurations of each compound were established by NMR spectroscopy.^{16, 157, 163}



SCHEME 4

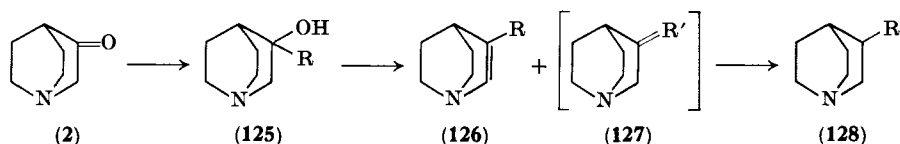
¹⁶⁰ G. Clemo and E. Hoggarth, *J. Chem. Soc.* 476 (1941).

¹⁶¹ M. V. Rubtsov, L. N. Yakhontov, and L. I. Mastafanova, *Zh. Obshch. Khim.* **33**, 1180 (1963).

¹⁶² C. A. Grob and J. Zergenyi, *Helv. Chim. Acta* **46**, 2658 (1963).

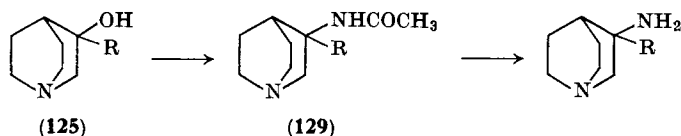
¹⁶³ J. C. Nouis, G. van Binst, and R. H. Martin, *Tetrahedron Letters* 4065 (1967).

Reaction between quinuclidin-3-one (**2**) and organolithium or organomagnesium compounds is a general method for preparing tertiary alcohols.^{47, 162, 164-168} By dehydration of these alcohols substances with a semicyclic double bond (**127**) are formed together with Δ^2 -dehydroquinuclidine derivatives (**126**).¹⁶⁵⁻¹⁶⁸ Reduction of unsaturated compounds gave various 3-substituted quinuclidines (**128**).



R = CH₃; C₂H₅; CH(CH₃)₂; —C(CH₃)₃; —CH₂—CH=CH₂; *i*-C₅H₁₁;
C₁₀H₇; C₆H₅CH₂—; C₆H₅—; *p*-C₆H₄N(CH₃)₂; *p*-C₆H₄OCH₃; *p*-C₆H₄OH

Acetonitrile with 3-alkyl(or aryl)-3-hydroxyquinuclidines (**125**) under Ritter reaction conditions has been used to prepare 3-acetamido-3-alkyl(aryl)quinuclidines (**129**).



An interesting method for the introduction of substituents into the 2-position of the quinuclidine ring starting from 3-substituted Δ^2 -dehydroquinuclidines (**126**) has been described.⁴⁷ By the reaction of methyl Δ^2 -dehydroquinuclidine-3-carboxylate (**130**) with isopropylmagnesium bromide, 1,4-addition with formation of 2-isopropyl-3-methoxycarbonylquinuclidine (**131**) took place instead of a sterically hindered Grignard reaction at the alkoxycarbonyl group.

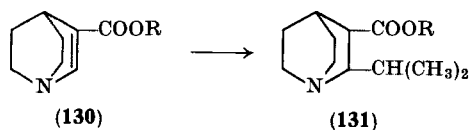
¹⁶⁴ L. Sternbach and S. Kaiser, *J. Am. Chem. Soc.* **75**, 6068 (1953).

¹⁶⁵ E. E. Mikhlin and M. V. Rubtsov, *Zh. Obshch. Khim.* **29**, 2337 (1959).

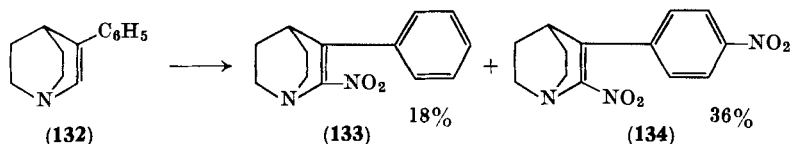
¹⁶⁶ G. van Binst, J. C. Noulis, and R. H. Martin, *Bull. Soc. Chim. Belges* **73**, 226 (1964).

¹⁶⁷ C. A. Grob, German (W) Patent 1,105,421 (1961); U.S. Patent 2,901,486 (1959); *Chem. Abstr.* **53**, 20098 (1959).

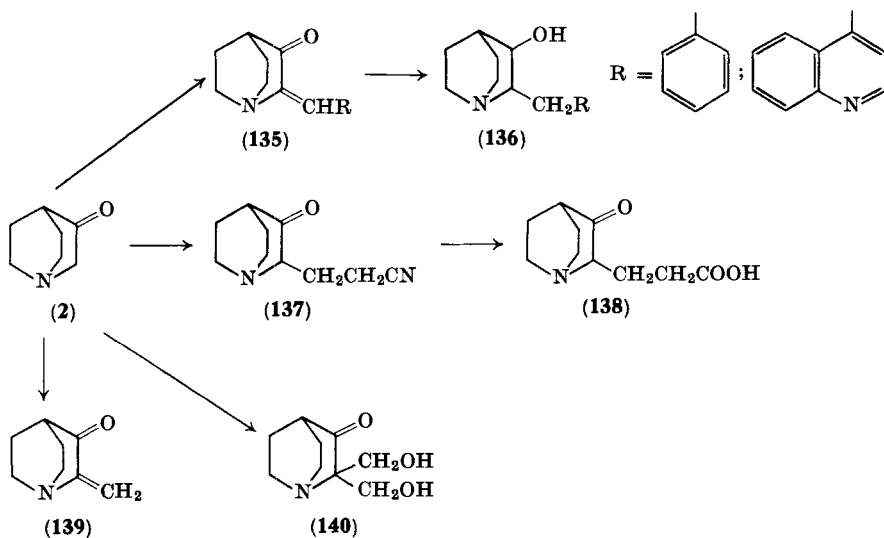
¹⁶⁸ C. A. Grob, German (W) Patent 1,105,422 (1961); U.S. Patent 2,917,515 (1959); *Chem. Abstr.* **54**, 8862 (1960).



Unusual 2-substituted quinuclidines were also obtained by nitration of 3-phenyl- Δ^2 -dehydroquinuclidine (132): 2-nitro-3-phenyl- and 2-nitro-3-(*p*-nitrophenyl)- Δ^2 -dehydroquinuclidines (133 and 134) were formed.⁴⁷



Syntheses of some 2-substituted quinuclidines utilized the high reactivity of the α -methylene group in quinuclidin-3-one (2) (Scheme 5). Condensations with aldehydes^{77, 103, 169} and acrylonitrile¹⁰⁴ led to 2,3-disubstituted derivatives. For example, the ketone (2) was converted into 2-benzylidene- and 2-(4-quinolylmethylene)quinuclidin-3-one (135) and then into 2-benzyl- and 2-(4-quinolylmethyl)-

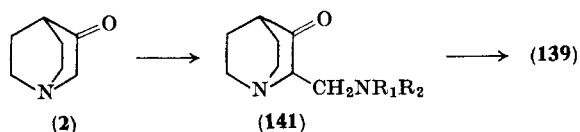


SCHEME 5

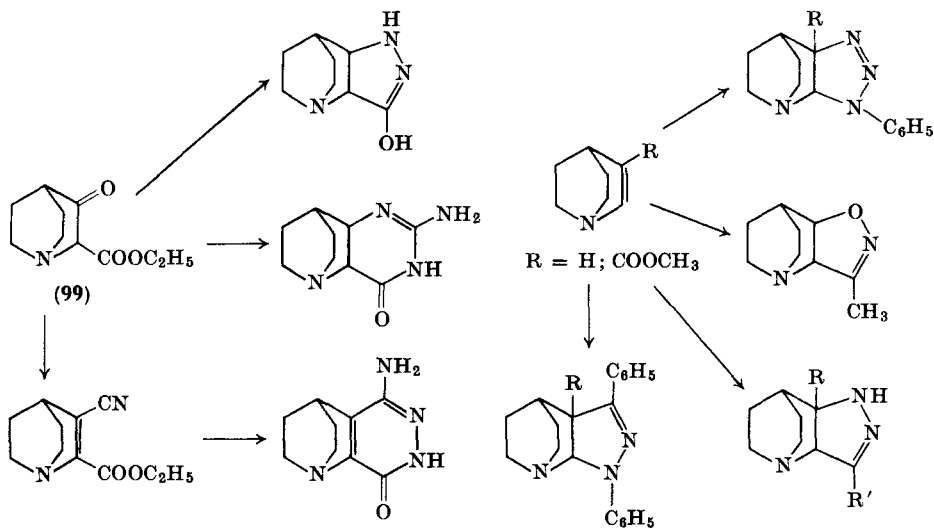
¹⁶⁹ G. Clemons and E. Hoggarth, *J. Chem. Soc.* 1241 (1939).

quinuclidin-3-ol (**136**), and also into 2-(β -cyanoethyl)-3-oxoquinuclidine (**137**), which gave β -(3-oxoquinuclid-2-yl)propionic acid (**138**). Condensation of quinuclidin-3-one (**2**) with formaldehyde gave 2-methylenequinuclidin-3-one (**139**); with an excess of the aldehyde 2,2-bishydroxymethylquinuclidin-3-one (**140**) was formed.⁷⁷

In the reaction of quinuclidin-3-one (**2**) with dimethylamine and formaldehyde, **141** spontaneously breaks down to 2-methylenequinuclidin-3-one (**139**).¹⁷⁰



Condensed heterocyclic systems containing a quinuclidine ring have been synthesized from ethyl 3-oxoquinuclidine-2-carboxylate (**99**), Δ^2 -dehydroquinuclidine (**4**), and methyl Δ^2 -dehydroquinuclidine-3-carboxylate: pyrazolo-, oxazolo-, triazolo-, pyrimido-, and pyridazinoquinuclidines have been made¹⁷¹ (Scheme 6).

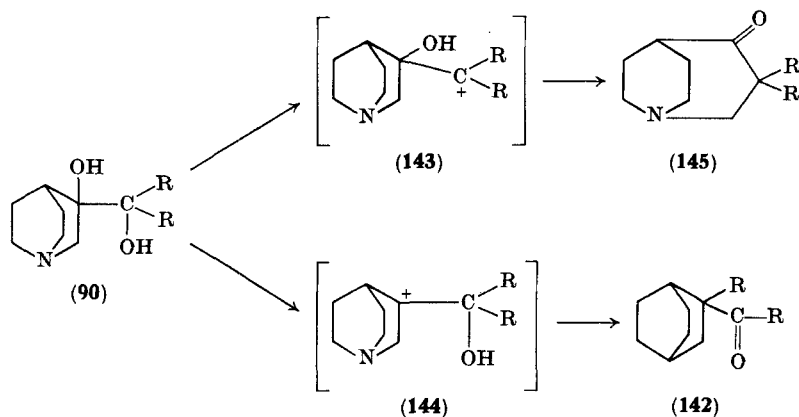


SCHEME 6

¹⁷⁰ A. R. Hansen and H. Bader, *J. Heterocyclic Chem.* **3**, 109 (1966).

¹⁷¹ W. A. Remers, G. J. Gibbs, and M. J. Weiss, *J. Heterocyclic Chem.* **4**, 344 (1967).

c. *Reactions with Quinuclidine Ring Expansion.* The pinacol rearrangement of *vic*-glycols of type (90) can give either ring-expansion products or quinuclidine ketones (142), depending on the substituents R and the reagents.^{144, 172} This is a result of the possibility of two



carbonium ions being formed (143 and 144) with electrophilic centers, respectively, at C-3 of the quinuclidine ring (144) and at the side-chain carbon (143). Subsequent migrations yield, in the first case, quinuclidine ketones (142) and, in the second case, 4-keto derivatives of 1-aza-bicyclo[3.2.2]nonane (145). Aryl substituents (R) stabilize the carbonium ions (143), and favor formation of products of type (145). Zinc chloride in acetic anhydride tends to yield carbonium ions of type (144) by the elimination of acetate ion from monoacetoxo derivatives initially formed. Hence in aprotic media quinuclidine ketones (142) or dehydration or acylation products of the starting glycols are formed.

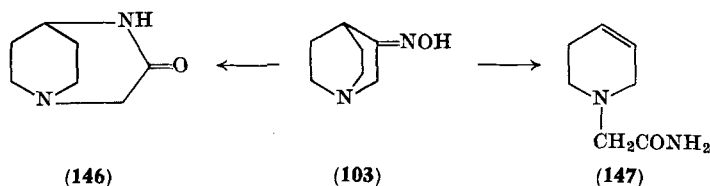
Beckmann rearrangement of quinuclidin-3-one oxime (103) in the presence of polyphosphoric acid or oleum proceeds with quinuclidine ring expansion and the formation of 3-oxo-1,4-diazabicyclo[3.2.2]nonane (146).^{173, 174} In polyphosphoric acid stabilization of the

¹⁷² A. D. Janina, E. E. Mikhлина, and M. V. Rubtsov, *Zh. Organ. Khim.* **2**, 1707 (1966).

¹⁷³ M. V. Rubtsov, E. E. Mikhлина, V. Ja. Vorob'eva, and A. D. Janina, *Zh. Obshch. Khim.* **34**, 2222 (1964).

¹⁷⁴ E. E. Mikhлина, V. Ya. Vorob'eva, V. I. Sheichenko, and M. V. Rubtsov, *Zh. Organ. Khim.* **1**, 1336 (1965).

intermediate cation is achieved, not only by C \rightarrow N shift of C-4, but also in part by C-3-C-4 bond cleavage with proton elimination from C-5. By the latter route the quinuclidine ring-cleavage product Δ^3 -dehydropiperidine-*N*-acetamide (147) is formed.



The same products were also obtained by treatment of quinuclidin-3-one (2) with hydrazoic acid under Schmidt reaction conditions¹⁷⁵; here the process gives mainly the monocyclic amide (147). Reaction of quinuclidin-3-one oxime (103) with arylsulfonyl chlorides in alkali leads to fragmentation and formation of *N*-substituted 3-cyanopiperidines.^{176, 177}

IV. Biological Properties of Quinuclidine Derivatives

Investigation of the biological properties of quinuclidine derivatives has proceeded mainly in two directions: (1) natural alkaloids, their synthetic analogs, and reaction products and (2) the pharmacological actions of compounds containing a quinuclidine ring. This review deals with the second aspect only; reference has already been made to several reviews devoted to the quinuclidine alkaloids.

The first research on the pharmacological action of unsubstituted quinuclidines was made by Stern in 1941.¹⁷⁸ In experiments on animals he established that quinuclidine hydrochloride causes a noticeable hypotensive activity and decreases the tone of smooth muscle. The corresponding quaternary salts display curarelike action.

In the course of investigations of quinuclidine and other 1-azabicycloalkane derivatives by Rubtsov *et al.*, several new methods for synthesis were found and many substances were prepared for bio-

¹⁷⁵ E. E. Mikhlin and M. V. Rubtsov, *Zh. Obshch. Khim.* **33**, 2167 (1963).

¹⁷⁶ H. P. Fischer, C. A. Grob, and E. Renk, *Helv. Chim. Acta* **42**, 872 (1959).

¹⁷⁷ C. A. Grob, H. P. Fischer, H. Link, and E. Renk, *Helv. Chim. Acta* **46**, 1190 (1963).

¹⁷⁸ P. Stern, *Arch. Exptl. Pathol. Pharmacol.* **197**, 377 (1941).

logical testing. Pharmacological testing of these substances by Mashkovskii and co-workers established the high activity of these compounds and found among them effective drugs for practical medicinal purposes.^{130, 179-192}

The testing of aminoalkyl quinuclidinecarboxylates, their quaternary halides, and tertiary amino derivatives of 2-mono-, 3-mono-, and 2,3-disubstituted quinuclidines revealed that several were active in breaking nerve transmissions at ganglions. Thus, ethyl quinuclidine-2-carboxylate (**73**) has a nicotineline activity. Certain 2-diethylaminoalkyl derivatives possess ganglion-blocking properties. Quaternary salts of dialkylaminoethyl quinuclidine-2- and -3-carboxylates are the most active ganglion-blocking agents; diethylaminoethyl quinuclidine-2-carboxylate bismethiodide (**148**), called Dioquine in the USSR, is one of the most potent of these agents.¹⁸⁴⁻¹⁸⁸ Three times more active than Dioquine is its dimethyl analog—dimethylaminoethyl quinuclidine-2-carboxylate bismethiodide. The corresponding 3-substituted compound has a similar action. Research into relationships between chemical structure and biological activity established that ganglion-blocking properties remain on going from the bicyclic

¹⁷⁹ M. D. Mashkovskii and M. V. Rubtsov, *Farmakol. Serd.-Sosud. Veschestv, Sb. (Kiev; Zdorov'e)* p. 103 (1965); *Chem. Abstr.* **65**, 20707 (1966).

¹⁸⁰ M. D. Mashkovskii, *Khim.-Farm. Zh.* **1**, No. 3, 3 (1967).

¹⁸¹ M. D. Mashkovskii, M. V. Rubtsov, E. E. Mikhлина, K. A. Zaitseva, and N. A. Komarova, Russian Patent 140,166 (1962).

¹⁸² M. D. Mashkovskii, M. V. Rubtsov, E. E. Mikhлина, and K. A. Zaitseva, Russian Patent 167,880 (1964); *Chem. Abstr.* **62**, 16000 (1965).

¹⁸³ I. M. Sharapov, *Farmakol. i Toksikol.* **25**, No. 6, 691 (1962).

¹⁸⁴ I. M. Sharapov, M. V. Rubtsov, E. S. Nikitskaya, M. D. Mashkovskii, and A. D. Janina, Russian Patent 118,775 (1959); *Chem. Abstr.* **53**, 22762 (1959).

¹⁸⁵ M. V. Rubtsov, E. S. Nikitskaya, and F. Ja. Leibel'man, *Materialy po Obmenu Peredovym Opytom i Nauchn. Dostizh. v Khim.-Farmatsevt. Prom.* No. 1, p. 46 (1959).

¹⁸⁶ I. M. Sharapov, *Med. Prom. SSSR* No. 6, 41 (1958); *Chem. Abstr.* **53**, 11657 (1959).

¹⁸⁷ I. M. Sharapov, *Farmakol. i Toksikol.* **20**, No. 6, 9 (1957).

¹⁸⁸ I. M. Sharapov, *Farmakol. i Toksikol.* **22**, No. 6, 512 (1959).

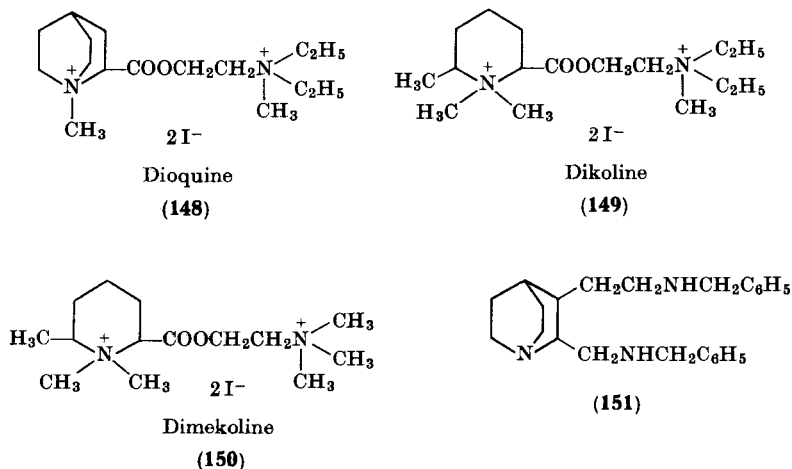
¹⁸⁹ M. V. Rubtsov, E. S. Nikitskaya, A. D. Janina, and V. S. Usovskaya, *Khim. i Med.* **15**, 16 (1960); *Chem. Abstr.* **58**, 4507 (1963).

¹⁹⁰ I. M. Sharapov, M. V. Rubtsov, E. S. Nikitskaya, M. D. Mashkovskii, and V. S. Usovskaya, Russian Patent 128,808 (1960).

¹⁹¹ I. M. Sharapov, E. S. Nikitskaya, M. V. Rubtsov, and V. S. Usovskaya, Russian Patent 213,263 (1962).

¹⁹² I. M. Sharapov, *Farmakol. i Toksikol.* **21**, No. 2, 18 (1958).

quinuclidine to the monocyclic piperidine system. Dimethylaminoethyl (149) and diethylaminoethyl 1,6-dimethylpipercolinate bis-methiodide (150), named Dimekoline and Dikoline,¹⁸⁹⁻¹⁹⁶ are used in the USSR as active ganglion-blocking drugs for the treatment of hypertonia, stomach ulcer, bronchial asthma, and some other conditions. Introduction of branched dialkylaminoalkyl groups instead of dialkylaminoethyl chains into the biologically active compounds decreases their ganglion-blocking activity.¹⁹⁷



It should be noticed that the activity of secondary amines like 2-benzylaminomethyl-3-(β -benzylaminoethyl)quinuclidine (151) depends on the presence of the bicyclic quinuclidine system, in contrast to the similar action of aminoalkyl quinuclidinecarboxylate quaternary salts. In this case transition to compounds without a quinuclidine ring removes their action on ganglions of the sympathetic and parasympathetic nervous systems.

In search of ganglion-blocking and curarelike compounds, diquaternary salts were synthesized and tested in which one (152)¹⁹⁸,

¹⁹³ I. M. Sharapov, *Farmakol. i Toksikol.* **21**, No. 1, 19 (1958).

¹⁹⁴ I. M. Sharapov, *Farmakol. i Toksikol.* **25**, No. 5, 533 (1962).

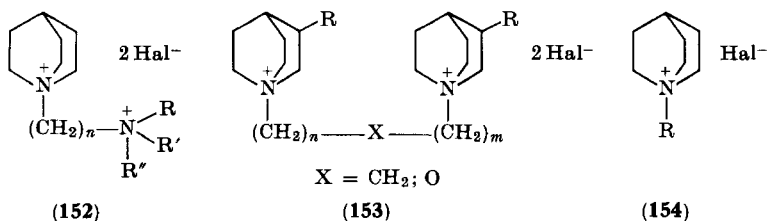
¹⁹⁵ I. M. Sharapov, *Med. Prom. SSSR*, No. 7, 55 (1960).

¹⁹⁶ I. M. Sharapov, *Farmakol. i Toksikol.* **24**, No. 6, 700 (1961).

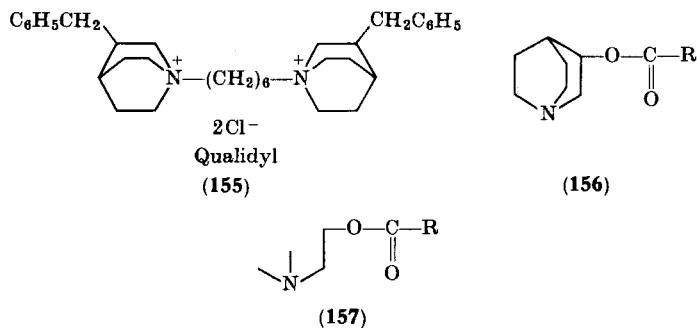
¹⁹⁷ M. V. Rubtsov, E. S. Nikitskaya, V. S. Usovskaya, and E. I. Levkoeva, *Khim.-Farm. Zh.* **1**, No. 3, 48 (1967).

¹⁹⁸ D. W. Coates, J. P. Buckley, and W. J. Kinnard, *J. Pharm. Sci.* **52**, 71 (1963).

¹⁹⁹ or both (153)²⁰⁰⁻²⁰² of the quaternary nitrogens, connected by polymethylene chains, were contained in quinuclidine rings, and also 1-alkylquinuclidinium halides (154; R=Alkyl)²⁰³ and *N*-aminoquinuclidinium salts (154, R=NH₂).²⁰⁴ The most active curarelike



(competition type) compound found was the derivative (155), used in the USSR under the name Qualidyl.^{200, 202}



Interesting pharmacological properties were discovered in 3-hydroxyquinuclidine esters (156), which can be considered as bicyclic analogs of the 2-dialkylaminoethyl esters (157). The neurotropic activity of these esters with various carboxylic acids is well known. Investigations of Sternbach, Kaiser, and co-workers^{103, 146-148, 164}

¹⁹⁹ J. H. Biel and A. E. Drukker, U.S. Patent 2,834,779 (1958); *Chem. Abstr.* **53**, 3251 (1959).

²⁰⁰ E. E. Mikhлина, V. Ja. Vorob'eva, and N. V. Rubtsov, *Zh. Obshch. Khim.* **31**, 2609 (1961).

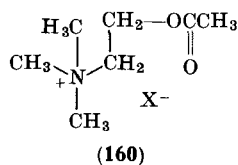
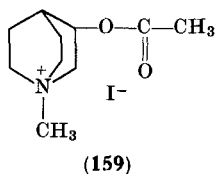
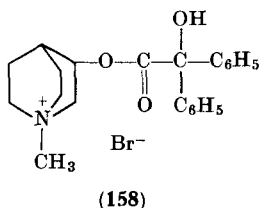
²⁰¹ F. Sadritdinov, *Farmakol. i Toksikol.* **25**, No. 3, 327 and 428 (1962).

²⁰² M. D. Mashkovskii and F. Sadritdinov, *Farmakol. i Toksikol.* **25**, No. 6, 685 (1962).

²⁰³ J. C. Kellett and C. W. Hite, *J. Pharm. Sci.* **54**, 883 (1965).

²⁰⁴ B. Rudner, U.S. Patent, 2,892,832 (1959); *Chem. Abstr.* **54**, 1561 (1960).

showed spasmolytic activity of 3-hydroxyquinuclidine esters with aromatic acids (benzilic, tropic, etc.). Almost at the same time Duschinsky found similar activity in substituted 3-carbamoyloxyquinuclidines.¹⁴⁹ 3-Benziloyloxy-1-methylquinuclidinium bromide (**158**) is in use as a cholinolytic drug under the names Clidinium bromide, Quazane bromide, or Marplan in the United States and some other countries.²⁰⁵⁻²¹¹



Systematic investigations of the pharmacological properties of 3-hydroxyquinuclidine esters and related substances were conducted by Mashkovskii and co-workers.¹⁷⁹⁻¹⁸⁰ They tested 3-acetoxy-1-methylquinuclidine (**159**) as a bicyclic analog of acetylcholine (**160**). Compound **159** had cholinomimetic activity, but is less active than acetylcholine. The corresponding tertiary amine 3-acetyloxyquinuclidine was much more active, and in contrast to acetylcholine had a more selective influence on muscarine receptors and penetrated the blood-brain barrier more easily. 3-Acetyloxyquinuclidine salicylate (**161**) is used in the USSR and some other countries in ophthalmology under the trade name Aceklidine^{181, 212, 213} for the treatment of glaucoma, and against postoperative atony of abdominal organs, and

²⁰⁵ R. R. Heffner, *N.Y. State J. Med.* **57**, 2214 (1957).

²⁰⁶ H. William, *J. Lab. Clin. Med.* **48**, 603 (1956).

²⁰⁷ L. O. Randell, N. M. Benson, and P. L. Stefko, *J. Pharmacol. Exptl. Therap.* **104**, 284 (1952).

²⁰⁸ C. Bell and S. Gershon, *Med. Exptl.* **10**, 15 (1964).

²⁰⁹ J. T. Carstensen, J. J. Vance, and G. Zbinden, U.S. Patent 3,122,474; *Chem. Abstr.* **60**, 11858 (1966).

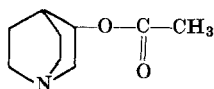
²¹⁰ J. A. Pianfetti, W. L. Johnson, and E. J. Orwoll, U.S. Patent 3,118,896; *Chem. Abstr.* **60**, 9254 (1964).

²¹¹ J. T. Carstensen and W. Valentine, Belgian Patent 623,704; *Chem. Abstr.* **60**, 10484 (1964).

²¹² M. D. Mashkovskii and K. A. Zaitseva, *Farmakol. i Toksikol.* **23**, No. 5, 398 (1960).

²¹³ K. A. Zaitseva and M. D. Mashkovskii, *Med. Prom. SSSR* No. 5, 42 (1961).

in particular for treating postnatal uterine atony. Subsequent investigation revealed that the cholinomimetic activity of Aceclidine depended to a considerable extent on the presence of the quinuclidine ring.^{151, 214, 215} Replacement of 3-hydroxyquinuclidine by any other



Aceclidine

(161)

bicyclic or monocyclic amino alcohol decreases or completely removes the pharmacological activity. Cholinomimetic action is decreased also by the introduction of alkyl groups at positions 6 and 8 of the quinuclidine ring.

Replacement of the acetyl group in Aceclidine by homologous acyl groups leads at first (propionic ester) to a decrease in cholinomimetic activity and then (butyric and isovaleric esters) to the appearance of cholinolytic properties.

Very strong cholinomimetic activity was found for 3-hydroxyquinuclidine esters with arylaliphatic acids. For example, 3-(α,α -diphenylpropionyloxy)quinuclidine (162) (which is known in the USSR as Aprodine²¹⁶⁻²¹⁸ significantly exceeds the similar 2-diethylaminoethyl ester (163) (in the USSR Aprophen) in its influence on the central and peripheral cholinergic systems.²¹⁹

3-Aroyloxyquinuclidines are noted for their sedative action on the central nervous system, for example, 3-benzoyloxyquinuclidine, is used in the USSR as the hydrochloride (164) under the tradename Oxyldine.^{182, 220-226} Oxyldine is especially effective for mental

²¹⁴ K. A. Zaitseva, M.D. Mashkovskii, and A. F. Roshchina, *Farmakol. i Toksikol.* **27**, No. 6, 686 (1964).

²¹⁵ B. Hansen and A. Flormark, *Acta Chem. Scand.* **17**, 1481 (1963).

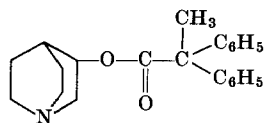
²¹⁶ M. D. Mashkovskii and K. A. Zaitseva, *Farmakol. i Toksikol.* **25**, No. 6, 679 (1962).

²¹⁷ M. D. Mashkovskii and K. A. Zaitseva, *Bull. Eksperim. Biol. (USSR)* **8**, 54 (1967).

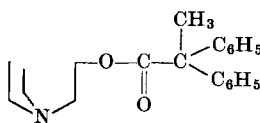
²¹⁸ K. A. Zaitseva, *Farmakol. i Toksikol.* **30**, No. 5, 597 (1967).

²¹⁹ M. D. Mashkovskii and K. A. Zaitseva, *Farmakol. i Toksikol.* **30**, No. 1, 36 (1967).

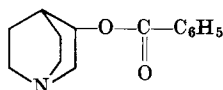
²²⁰ M. D. Mashkovskii, *Sov. Med.* **6**, 88 (1965).



Aprolidine
(162)



Aprophene
(163)



HCl
Oxylidine
(164)

derangements connected with abnormalities in cerebral blood circulation. At the same time it has a hypotensive effect and is used for hypertonia treatment. It should be noticed that the high biological activity of other 3-hydroxyquinuclidine esters, as in the case of Aceclidine, depends on the presence of the quinuclidine azabicyclic system. The corresponding 3-hydroxypiperidine esters (**165**), esters of *N*-alkyl-*N*-cycloalkylaminoethanols (which can be regarded as ring-opened 3-hydroxyquinuclidine compounds), and esters of other hydroxy-1-azabicycloalkanes, 1-aza-6-hydroxybicyclo[3.2.1]heptane (**166**) and 1-aza-4-hydroxybicyclo[3.2.2]nonane (**167**), have much less pharmacological effect.

Probably the high biological activity of 3-hydroxyquinuclidine derivatives, in comparison with those of other similar mono- and bicyclic aminoalkanols, is a result of the absence of steric hindrance of the nitrogen lone-pair electrons. Interaction of these electrons with electrophilic centers of the corresponding biochemical receptors, in the opinion of some authors,²²⁷ accounts for the higher psychotropic

²²¹ M. V. Rubtsov, E. E. Mikhлина, N. A. Komarova, V. Ja. Vorob'eva, and L. Sh. Gorodetskii, Russian Patent 176,898 (1965); *Chem. Abstr.* **64**, 12652 (1966).

²²² K. A. Zaitseva, *Med. Prom. SSSR* No. 2, 58 (1966).

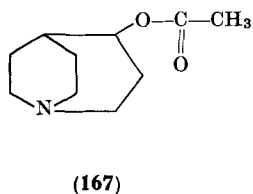
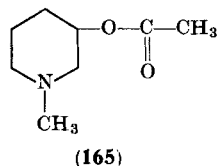
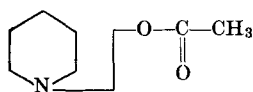
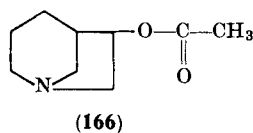
²²³ M. D. Mashkovskii and K. A. Zaitseva, *Farmakol. i Toksikol.* **25**, No. 1, 32 (1962).

²²⁴ M. D. Mashkovskii and L. F. Roshchina, *Zh. Nevropatol. i Psikiatr.* **63**, 1532 (1963).

²²⁵ L. F. Roshchina, *Farmakol. i Toksikol.* **27**, No. 6, 659 (1964).

²²⁶ A. Zakhdi, *Farmakol. i Toksikol.* **27**, No. 1, 17 (1964).

²²⁷ N. W. Gabel and L. G. Abood, *J. Med. Chem.* **8**, 616 (1965).



activity of 3-benziloyloxyquinuclidine in comparison with esters of other *N*-substituted amino alcohols. At the same time intermolecular interactions are very unlikely in 3-hydroxyquinuclidine esters, the acyl part of which is firmly held away from the lone-pair electrons.

It is to be expected that further investigations will reveal more completely the relationship between the pharmacological effects and the chemical structure of quinuclidine derivatives and their conformation, the character of the lone-pair electrons at the nitrogen atom, and so on, and that this will lead to the discovery of new pharmacologically active compounds.

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